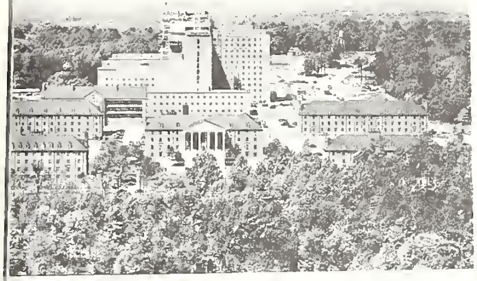
NIH Library, Building 10
National Institutes of Health
Bethesda, MD 20892

NI
Na
Bet

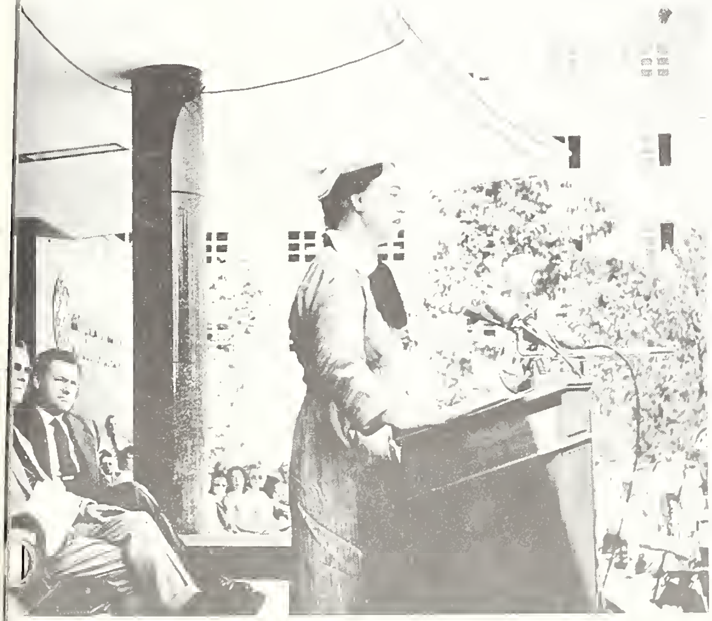
NEWS&FEATURES FROM NIH

PORTFOLIO - CLINICAL CENTER 25TH ANNIVERSARY

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE■Public Health Service■National Institutes of Health■Office of Information■Bethesda, Maryland 20014



LIBRARY
JAN 12 1979
NATIONAL INSTITUTES OF HEALTH

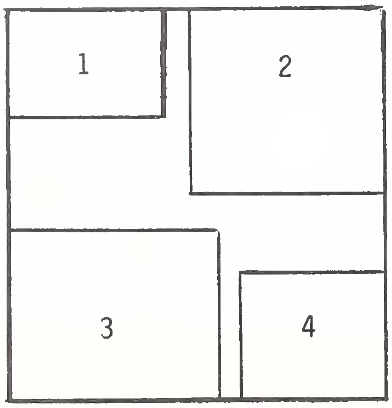


JANUARY 1979

Marc Stern, Editor
Thomas H. Flavin, Associate Editor
NIH News Branch
Building 31, Room 2B-10
Bethesda, MD 20014
Phone: (301) 496-1206

Designed by Joyce F. McCarthy

PORTFOLIO: 25th ANNIVERSARY OF THE CLINICAL CENTER



COVER
PHOTOS

(1) The Clinical Center in the final stages of construction. (CP-1)

(2) President Harry S. Truman, trowel in hand, prepares to lay the cornerstone for the Clinical Center on June 22, 1951. The three men in the first row behind the President are (l. to r.) Dr. William H. Sebrell, Jr., then NIH Director; Contractor John McShain; and Dr. Leonard A. Scheele, USPHS Surgeon General. (CP-2)

(3) Mrs. Oveta Culp Hobby, Secretary of Health, Education, and Welfare, dedicated the Clinical Center on July 2, 1953. Seated behind her are the Rev. Dr. Frederick Brown Harris, chaplain of the U.S. Senate; and Nelson A. Rockefeller, then Under Secretary of DHEW. (CP-3)

(4) The Clinical Center as it is today. (CP-4)

The Clinical Center, in the right upper quadrant of this aerial view, dominates the 306-acre National Institutes of Health "campus". (NIH Photo #CC-1)

PORTFOLIO: 25th ANNIVERSARY OF THE CLINICAL CENTER

INTRODUCTION

A visiting foreign scientist working at the Clinical Center in this, its 25th year, was overheard to say, "What is hard to comprehend is that the amount of research done in this building in one week is equal to all the medical research done in my country in one year."

With over 2,300 employees devoted to biomedical exploration and clinical excellence, the volume of work done at the Clinical Center indeed makes it unique. But what makes it most special, perhaps is the setting in which that work is done. There are 541 hospital beds, with twice as much space devoted to laboratories as to patient care areas. This means that biochemists peering down microscopes at proteins isolated from diseased lungs can hear patients with emphysema coughing across the hallway. And neurophysiologists studying nerve axons in squids glance occasionally at television monitors taping epileptic seizures in infants. Pediatricians sit down to coffee in the cafeteria with molecular biologists and biostatisticians as children skim by in wheelchairs.

There have been many research achievements made at the Clinical Center in the past twenty-five years. Its greatest achievement may have been simply to be here, to be the setting where the patients' presence, amid so much scientific brilliance, prevented its becoming an ivory tower and made the Clinical Center instead a place of care and creativity.

THE CLINICAL CENTER

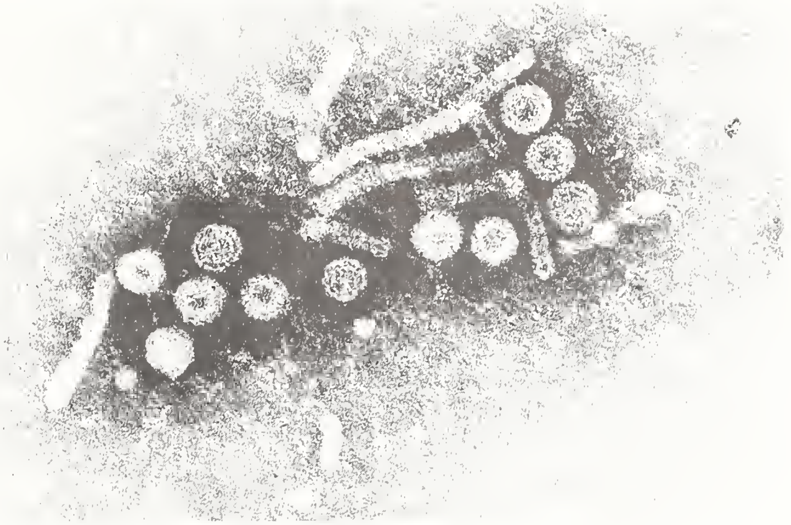
Physically the Clinical Center is a 14-story red brick building, with each of twelve stories accommodating approximately twenty-five patients and one hundred laboratories. The Center was specially designed to bring patient care facilities close to research laboratories so that the new findings of basic and clinical scientists can be moved quickly from the labs to the treatment of patients.

Nearly one thousand physicians from the eleven NIH institutes conducting research at the Center provide the medical care. Nursing care and other support services are provided by Clinical Center staff.

Patients, upon referral by their physicians, are admitted to clinical studies conducted by the Institutes. Over six thousand patients are treated as fulltime admissions annually, and with the completion of the new addition in the early 1980's, the Clinical Center will accommodate over 300,000 outpatients visits.

The high quality of medical and support care required for clinical research at the Center have led to innovations that have influenced patient care throughout the nation. This portfolio will touch on but a few of them.

CONQUERING HEPATITIS



The Dane particles and filamentous form of hepatitis B antigen are shown in this photomicrograph magnified 150,000 times. (NIH Photo #CC-2)

Significant advances have been made in the control of post-transfusion hepatitis since the Clinical Center opened its doors in 1953. A large number of these advances are due to the Center's Blood Bank.

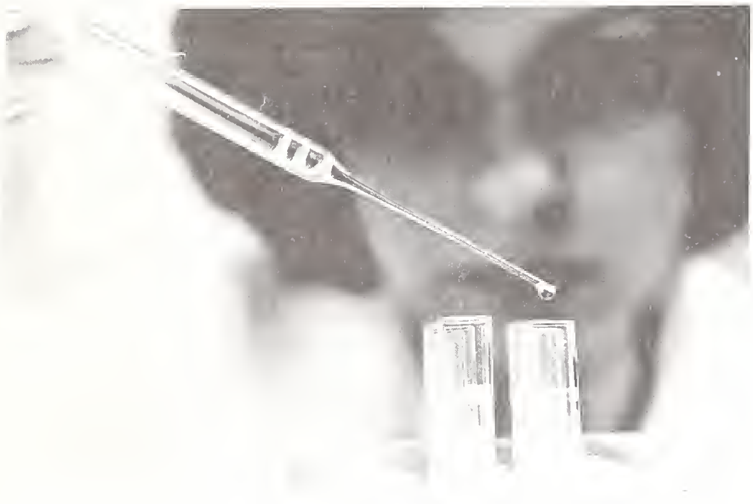
As early as 1957 the Blood Bank had published its first research paper delineating the post-transfusion hepatitis problem, firing the first salvo in what was to be a long but largely successful campaign.

In 1964 an antigen - the Australia antigen - was discovered, first in a blood sample collected from an aborigine and then in the blood of leukemia patients by Blood Bank Immunology Chief Dr. Harvey Alter and National Cancer Institute investigator Dr. Barruch Blumberg. Later Dr. Blumberg, who was then working in Philadelphia, linked the antigen with hepatitis. For this discovery he was awarded the Nobel Prize.

Paralleling this laboratory work was a clinical study conducted by the Blood Bank that was published in 1970. Patients undergoing open-heart surgery at the Clinical Center were divided into two groups, one that received commercial blood, the other group that received blood from volunteers who had donated at the Clinical Center or the Washington Red Cross Center. Within six months after the operation, over 50% of those receiving commercial blood developed hepatitis. No hepatitis developed in those receiving voluntary blood. With this concrete evidence in hand, the Clinical Center implemented a supply program that relied exclusively on voluntary blood provided by NIH employee donors and the Red Cross.

Subsequently Blood Bank Chief Dr. Paul Holland, working with other researchers in the Blood Bank, the National Institute of Allergy and Infectious Diseases, and the National Heart, Lung, and Blood Institute, demonstrated in another clinical study that transfused blood containing the antigen often results in patients getting hepatitis. These studies laid the foundation for the current FDA ruling that every blood unit be tested for the antigen - now called hepatitis B surface antigen (HBsAg) - before transfusion.

With the sole use of volunteer donors and hepatitis screening with a radioactive test for the hepatitis B antigen, it was hoped that the blood from the Blood Bank would soon be hepatitis free. This was not the case. Instead, 8% of the transfused patients continued to develop hepatitis after transfusions. This frustrating experience prompted the most recent and perhaps most important discovery made at the Blood Bank - the identification of a new form of viral hepatitis, called non-A, non-B hepatitis. Dr. Alter and his colleagues have developed an animal model for this newly recognized disease. The Blood Bank researchers are currently attempting to develop a test to identify carriers of non-A, non-B hepatitis who may inadvertently transmit this disease to patients through their blood donations.



A Blood Bank technician prepares blood samples for analysis.

At a press conference on March 27, 19 Dr. Tabor of the FDA Bureau of Biolog and Dr. Alter of the CC Blood Bank announce that their independent stud have demonstrated for the first time that a transmissible agent is respons for non-A, non-B hepatitis.

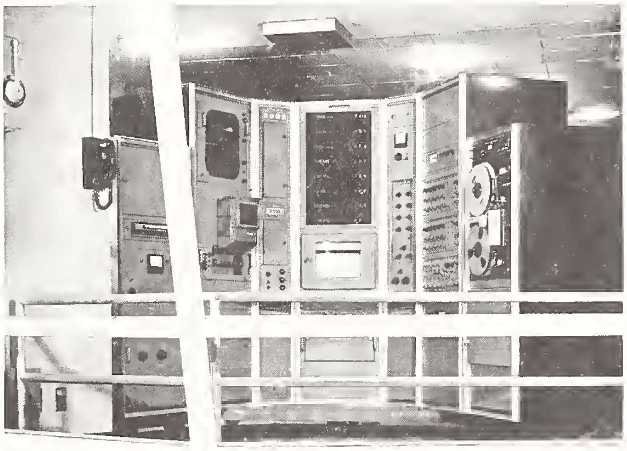
SURGERY IN THE ROUND

No overview of Clinical Center highlights would be complete without touching on the surgical successes and advances achieved there.

In 1953 as part of its initial structure, the Clinical Center had standard operating theaters that were up-to-date but otherwise unremarkable. It was here that Dr. Andrew G. Morrow, who has been Chief of Cardiac Surgery since the Clinical Center opened its doors, began his early work in open heart surgery that culminated in 1960 with the very first successful removal and replacement of the mitral valve in the human heart.

Construction of a new surgical wing began in 1959 and was completed in 1963. It was innovative from its circular exterior to its theaters within that permit neurosurgery to be viewed by outsiders from less than seven feet away and open-heart surgery to be conducted with a team half the usual size. Foreshadowing our digital age, display boards were installed in each theater to provide instant information about a patient's condition on a 24-channel monitor.

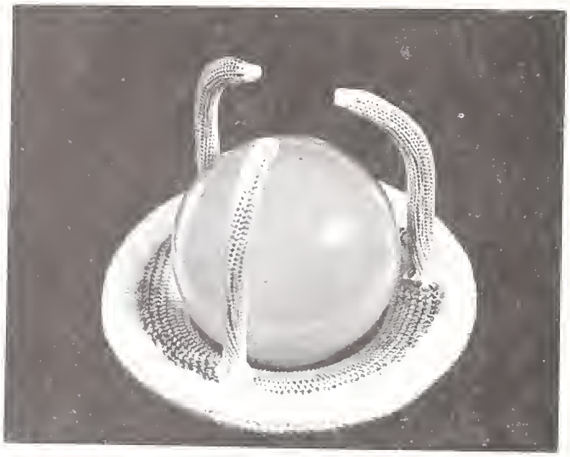
ough a porthole in the observation k of one of the operating theaters, a tographer records the techniques used open heart surgery.(NIH Photo #CC-3)



The instrumentation console in the cardiac recording room displays data on a patient's heart rate, blood pressure, blood loss, etc., on the screen in the center. To the left, on the oscilloscope screen, waveforms of the same information appear. (NIH Photo #CC-4)

The valve used by Dr. Morrow in 1960 was developed by him and Dr. Nina S. Braunwald. It was made of flexible plastic and was designed to mimic the natural mitral valve. The valve was difficult to place within the heart, however, and was supplanted in that same year by the ball valve developed by Dr. Albert Starr and engineer M.L. Edwards at the University of Oregon. The Starr valve was rugged and dependable but a major drawback was the origin of blood clots from the bare metal arms of the cage which enclosed a silicone rubber ball. Such clots occurred in spite of treatment of the patient with anticoagulants.

Hancock porcine xenograft.
(NIH Photo #CC-5)



Fabric-covered Starr-Edwards valve.
(NIH Photo #CC-6)

Investigations at the Clinical Center's Surgery Branch and elsewhere found that the clotting problem could be alleviated by covering the cage arms with a teflon-type fabric. This improved design, the cloth-covered Starr-Edwards valve, was first implanted in a patient by Dr. Morrow, in the new Surgical Wing of the Clinical Center in February 1967. By December of 1968, more than one hundred patients had received the improved valve at the Clinical Center. Follow-up studies have since confirmed that the fabric covering indeed markedly reduces the clotting problems.

During the same period further research was being done on other suitable materials and sources for artificial valves. A promising development was a pig heart valve preserved and sterilized by glutaraldehyde and mounted on a flexible polypropylene frame or "stent." This design is known as the Hancock porcine xenograft, named after W.D. Hancock who perfected this valve configuration with Dr. Robert Reis and Dr. Morrow at the NIH.

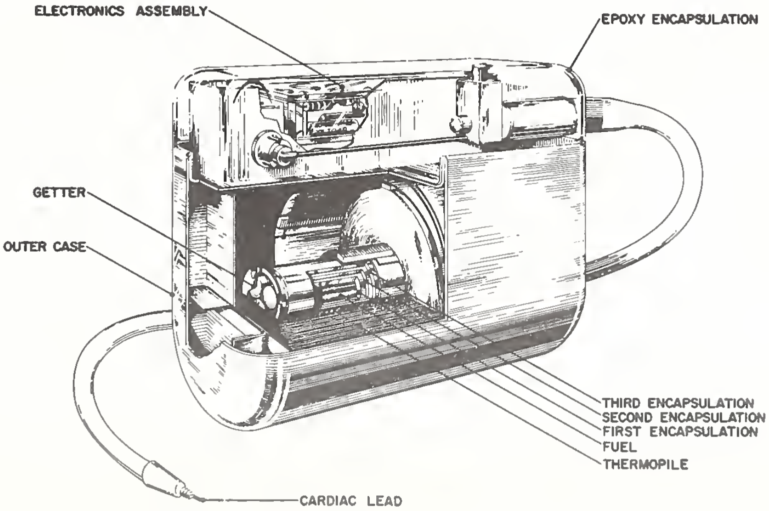
The Hancock xenograft was first used to replace a mitral valve in a patient at the Clinical Center in July of 1970. The porcine valve has proven itself to cause far fewer clotting problems, so much so that anticoagulant drugs are not usually prescribed for its recipients as they usually are for other valve replacement patients. The Hancock valve also seems not to cause hemolysis, the destruction of red blood cells by the rougher surfaces of other artificial valves which necessitates iron supplementation. Its size makes it especially suitable for mitral valve replacement where space limitations are an important factor. Its only drawback may be in durability, but this seems less likely as more and more early recipients cross the critical five-year period without valve failure.

Another area of contribution by the National Heart, Lung, and Blood Institute's Surgery Branch has been in the design of artificial pacemakers. When one or more of the major elements of the heart's own conduction system are disrupted by disease or injury, heart block of varying degrees of severity may result. Normal heart rate and pacing can be restored in these patients by artificial pacemakers. These compact devices, which are implanted in the chest cavity, are usually powered by mercury batteries which must be replaced every two or three years. Though a simple operation, this replacement is not without risk of infection or other complication and it adds to a patient's expenses.

It was Dr. Andrew Morrow who first conceived of using a nuclear power source, plutonium 238, to extend a pacemaker's useful life from 11 to 20 years. Such a pacemaker power cell was subsequently developed under contract by the Atomic Energy Commission. The capsule, which contained the radioactive plutonium, withstood a whole battery of tests such as point blank impact from a .44 magnum handgun and a simulated cremation at 1,000° C.

After extensive testing in dogs, the first of these pacemakers was implanted by Dr. Charles McIntosh, in a patient in the Clinical Center in April of 1973. The patient had received her first conventional pacemaker in 1962 and had undergone 10 pacemaker-related operations in the following decade. Since that time, the nuclear-powered pacemakers have shown themselves to be particularly suitable for younger patients who have a longer life expectancy and thus can derive full benefit from the lengthy service and reduced operating costs.

Apart from these remarkable contributions in devising artificial parts for the heart, the cardiac surgery unit has also made important advances in corrective surgery for various congenital malformations. A good example of these advances are the strategies and techniques used to treat idiopathic hypertrophic subaortic stenosis (IHSS), a genetically transmitted disease of the heart muscle. In all cases of IHSS, the ventricular septum (the wall between the ventricles) is thickened, especially in the vicinity of the aortic valve, through which all blood destined for the systemic circulation must pass.



RADIOISOTOPE POWERED CARDIAC PACEMAKER NU-5

Studies now in progress indicate that IHSS may become clinically manifest in infancy, may be a factor in sudden infant death, or may lead to heart failure and death in the early months of life. It appears that IHSS may be more common than generally supposed but it is often difficult to detect by techniques other than echocardiography.

In some 10 to 15 percent of patients with IHSS, the septal thickening may seriously impede the flow of blood through the aortic valve, resulting in severe symptoms and eventually leading to congestive heart failure, fainting, or chest pain.

Because the obstruction is localized it is amenable to surgical treatment, but only by the always delicate procedure of open-heart surgery. Dr. Morrow devised the operation that removes the offending thickening of tissue from the septum and corrects the impeded flow of blood.

The long-term results are testimony to the success of this operation. After more than two hundred operations on patients with obstructive IHSS, the outflow obstruction has not recurred in a single patient.

The late President Lyndon B. Johnson toured the Clinical Center in August 1967. During the visit, Dr. Andrew G. Morrow, Chief of the NIH Surgery Branch, explained the surgical procedures used in valve replacement surgery as a simulated open-heart operation is performed below.

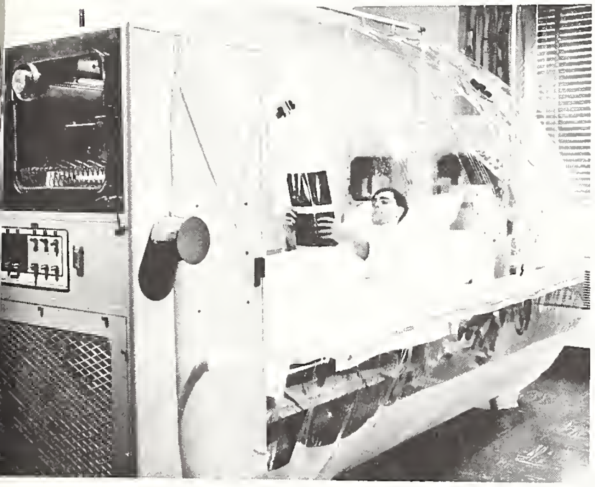
FROM LIFE ISLAND TO THE SPACE SUIT

The Clinical Center has been the site of some of the most effective treatments developed for specific forms of cancer. The first successful cure of a solid tumor with anticancer drugs was achieved in 1955 by Drs. Roy Hertz and M.C. Li. Drs. Mortimer B. Lipsett and Griff T. Ross, who are now Director and Deputy Director of the Clinical Center, extended these studies. They reported that choriocarcinoma, a rare cancer of the placenta that can occur following pregnancy, is almost entirely curable by chemotherapy if it is detected soon after it has developed.

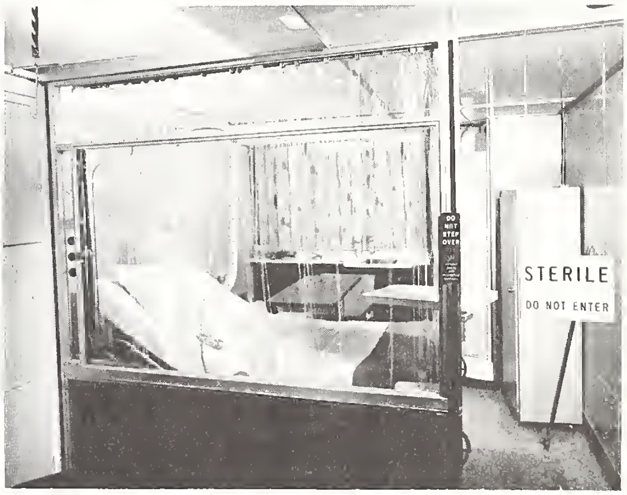
Similar chemotherapeutic successes have subsequently been reported by other National Cancer Institute investigators working at the Clinical Center, particularly in acute childhood leukemia and in Hodgkin's disease.

A common problem shared by many forms of cancer chemotherapy and some other treatment regimens is that these treatments interfere with the body's immune system, rendering the patient defenseless against infection. Leukemia patients are in double jeopardy because the disease itself interferes with the immune system. Despite the use of antibiotics, infection is ultimately responsible for about 70% of all deaths in acute leukemia.

In the 1960's the NCI, using methods first developed for breeding germ-free laboratory animals, began experimenting with different forms of patient isolation in order to prevent infection. The first system put into use at the Clinical Center in 1965 was a soft, clear plastic canopy that enclosed the hospital bed. This "Life Island" was moderately effective but severely restricted patient activity.



A patient reads a sterilized magazine in one of the first "Life Island" isolators used by the Clinical Center in the mid-1960's. (NIH Photo #CC-7)



The laminar airflow room, originally designed to assemble space capsules and instruments for use in the NASA program, has a more efficient air filtration system and allows for more patient mobility. (NIH Photo #CC-8)

(NIH Photo #CC-9)

(NIH Photo #CC-10)

The isolator itself must be thoroughly cleaned and sterilized by the Clinical Center nurses. The patient, too, must be made as germ-free as possible. Starting two or three days before entering, she is given numerous baths and showers. After each bathing, a complete change of bed clothes and linen is made. Even the patient's internal system is specially prepared for germ-free living. All items must be sterilized before being placed in the isolator. Sterile emergency equipment must be on hand in the "Life Island" room, which must also be kept germ-free. All the patient's food and beverages are specially prepared and sterilized.

Laminar air flow rooms were originally constructed to assemble space capsules and instruments in a particle-free atmosphere. The cancer researchers applied this technology to patient isolation, and the first prototypes were assembled and successfully operated at the Clinical Center in June of 1968. The laminar air flow rooms utilize plastic sheeting, a "curtain" of flowing air, and a highly efficient air filtration system to greatly increase patient mobility while maintaining very effective isolation and filtration.

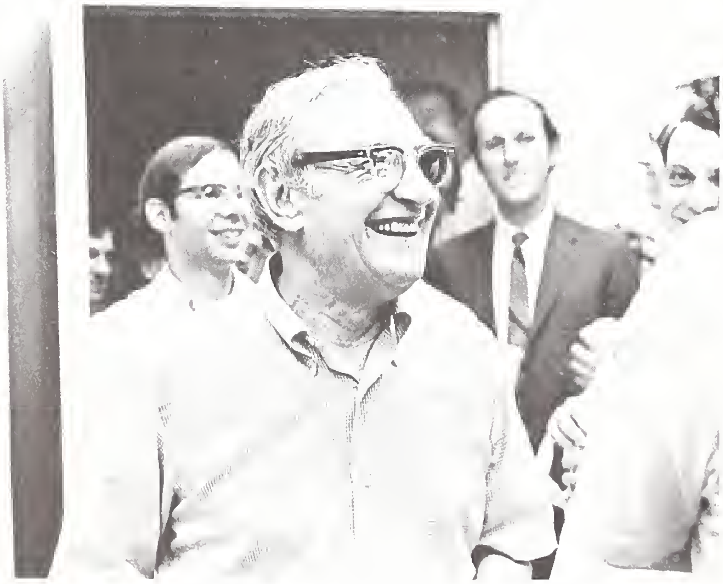
However, the NCI alliance with space technology was far from over. In April of 1976 the most recent advance in isolation technology was tested in prototype at the Clinical Center - an altered descendant of the biological isolation garments worn by the astronauts of Apollo 11, 12, and 13. This "space suit" packs its own battery-powered air filtration and positive-pressure systems into a minimal 6 pounds, and permits the wearer to leave the hospital for several hours at a time. The fabric is a high-density cotton poplin developed by NASA that permits the outward rush of air but prohibits the influx of particulate matter. The suit restores some elements of a nearly normal, active existence for those patients who must undergo long periods of immune deficiency and laminar flow room isolation. The value of the laminar air flow rooms and the space suit is not limited to cancer patients. Burn victims, persons receiving organ transplants, and others on immunosuppressive drugs may benefit from isolation engineering concepts first tested at the Clinical Center.

Another treatment that is effective in some cancer patients who develop infection is white blood cell transfusion. Physicians at the NCI pioneered in the development of centrifuges capable of continuously recovering white cells from normal blood donors and replacing the remainder of the blood. These white cells can then be used in patients with serious infections whose own white cells have been destroyed by the therapy. These techniques are now part of the Clinical Center armamentarium to support cancer patients.

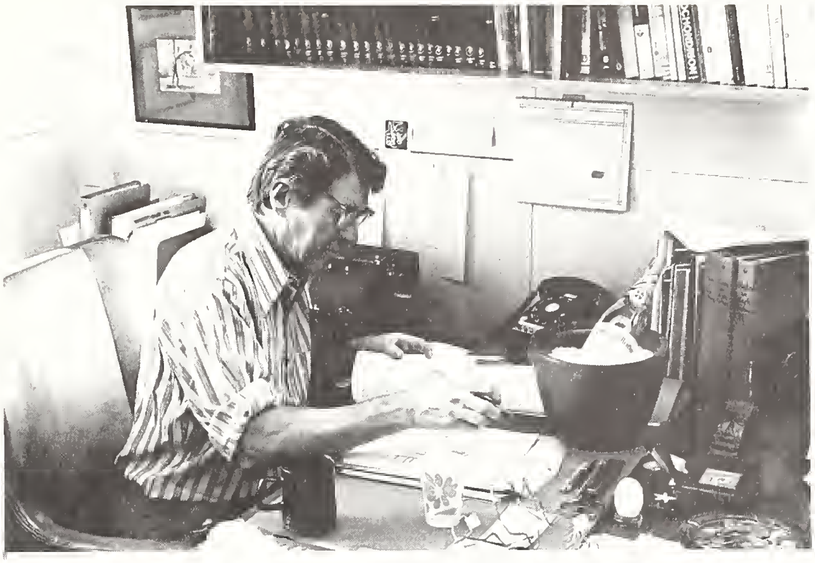
To make physical freedom possible without jeopardizing the protection of patients, the development of a mobile germ-free environment was designed by scientists at the National Cancer Institute in cooperation with NASA and private industry. The "space suit" is an altered descendent of the biological isolation garments worn by astronauts of Apollo flights 11, 12, and 13. This sterile suit operates on principles similar to those of the laminar airflow rooms.

FOUR NOBEL PRIZE WINNERS

Dr. Marshall W. Nirenberg (center) at the 1968 award ceremonies in Stockholm. He received his prize for discovering the key to deciphering the genetic code, leading the way to recombinant DNA research.



Dr. Julius Axelrod in the hallway of his Clinical Center lab after hearing word of his winning the 1970 Prize for Physiology or Medicine. His research traced the function of catecholamines in the brain and how these chemical messengers are affected by various antidepressant drugs.



With a champagne bottle in his 9th floor Clinical Center office, Dr. Christian B. Anfinsen prepares to call his co-winners of the 1972 Chemistry Prize. Dr. Anfinsen's work contributed enormously to the first artificial synthesis of an enzyme, ribonuclease, which catalyzes the breakdown of RNA. This discovery led to a better understanding of metabolic disorders.

Dr. D. Carleton Gajdusek meets the press in the Clinical Center auditorium after the announcement of his winning the 1976 Prize for Physiology or Medicine. He discovered a new, highly unusual virus form that slowly destroys the nervous system over the years. These "slow viruses", which he proved caused kuru, the fatal "shivering" disease of certain New Guinea natives, are transmissible and may be responsible for some forms of central nervous system disease and multiple sclerosis.

Dr. Gajdusek confers with fellow laureates Nirenberg and Axelrod after the press briefing.

DIAGNOSTIC IMAGING

Early and detailed diagnosis is often the key to effective treatment. A picture or image can truly be worth the proverbial thousand words in helping the physician make such a diagnosis. The Clinical Center has two departments, Diagnostic Radiology and Nuclear Medicine, that are concerned with the production of diagnostic images. Their successes have been so many and varied that it is possible to touch on only a few.

In 1964 Dr. John L. Doppman, now Chief of Diagnostic Radiology, and his associates reported the first successful imaging of the arteries that supply the spinal cord. The technique, known as spinal angiography, has made surgical intervention possible where spinal arterial malformations, lesions, or tumors cause paralysis. The researchers also experimented at this time with embolization (deliberate blockage) of the offending spinal arteries by injecting a clotting agent through the catheter that carries the radiologic contrast medium. Embolization can frequently eliminate the need for subsequent surgery. The technique is also used in cancer patients to decrease the pain caused by untreatable or unresponsive tumors.

Dr. Doppman and his associates in 1968 developed a method for locating the parathyroid, a group of glands, each about the size of a BB pellet, that regulates calcium metabolism. These glands are usually found in the neck behind the thyroid. Determining the precise location of a diseased parathyroid is a difficult and frustrating exercise but a critical one for successful surgery. The method developed at the Clinical Center is called "selective venous catheterization". The veins that drain the thyroid gland are sampled by a fluoroscopically directed catheter. The blood samples drawn are tagged by location and subjected to the sensitive radioimmunoassay for the presence of parathyroid hormone. When the levels of the hormones are higher than those in the peripheral blood, this pinpoints the location of the gland or tumor and suggest whether multiple glands are involved in the overproduction of hormones. The technique has been proven nearly 100% accurate in patients with newly diagnosed parathyroid disease.

Radionuclide cineangiography allows the heart to be viewed during and just after intense exercise. The patient is pedaling an exercise machine while a scintillation camera collects data for the compute based movie of his heart. (NIH Photo #CC-11)

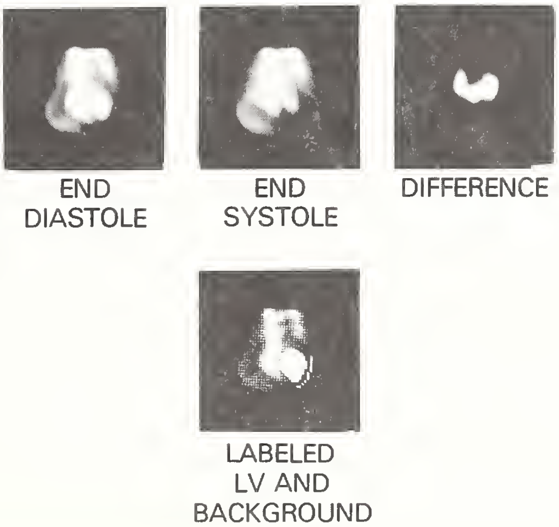
Researchers in the Nuclear Medicine Department have made similar progress in diagnosing heart and lung disease. In 1976 Dr. Jeffrey S. Borer of the National Heart, Lung, and Blood Institute, Dr. Michael V. Green and Dr. Stephen L. Bacharach of the Department of Nuclear Medicine, and members of the Division of Computer Research and Technology Medicine completed the development of radionuclide cineangiography. This technique permits viewing the heart by computer-based movies during and immediately after exercise.

Serum albumin tagged with a radioactive label is injected into a peripheral vein of the patient. A few minutes later a scintillation camera is placed over the patient's chest and begins measuring radioactivity emissions. Data are stored by a computer while the patient is at rest or exercising. The emissions can be displayed simultaneously as a motion picture and as a time-activity curve indicating precise changes in ventricular volume with time.

Using this method the investigators have been able to detect coronary artery disease even in patients who have normal cardiac function when at rest. In patients with known disease, researchers have been able to assess the severity of impairment and to evaluate the effects of therapy. The technique causes little discomfort, offers less risk than cardiac catheterization, and unlike catheterization, can be performed during exercise.

In 1977, using similar techniques, the team at Nuclear Medicine, NHLBI, and Dr. Bruce R. Line of the Division of Computer Research and Technology completed the development of pulmonary scintigraphy, which visually and graphically displays the functions of specific regions of diseased lung in patients affected by pulmonary fibrosis, emphysema, and other lung diseases.

The patient's air supply is tagged with radioactive xenon as the patient breathes from a spirometer. At the same time the pulmonary blood supply is labeled by an injection of technecium-macroaggregated albumin. The labeled albumin particles are larger than the pulmonary capillaries and are temporarily trapped there during measurement.



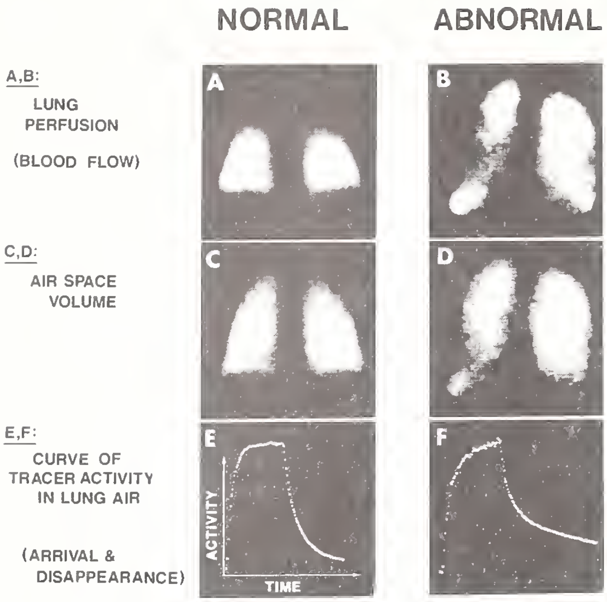
END DIASTOLE

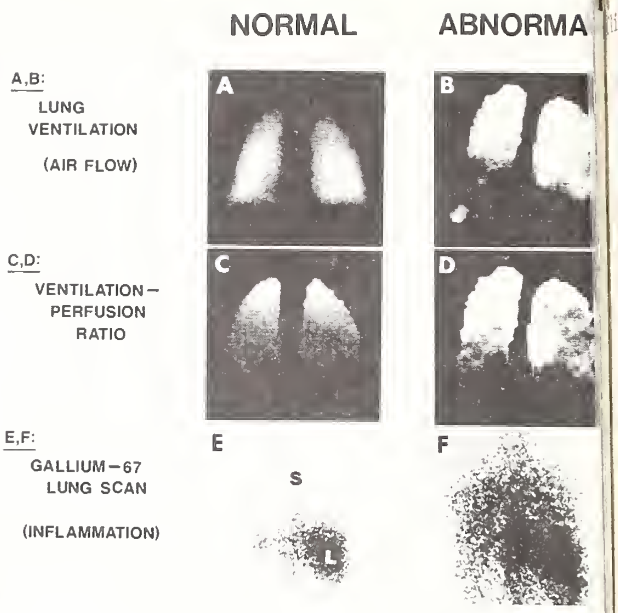
END SYSTOLE

DIFFERENCE

LABELED LV AND BACKGROUND

Selected frames from a radionuclide cineangiogram. The end diastole shows the heart at its maximum fill and the end systole shows the heart in maximum contraction. The "difference" represents that fraction of blood pumped by the heart in the previous two frames. The labeled LV and background is the left ventricle isolated from the other pumping chambers of the heart. (NIH Photo #CC-12)





Gamma rays emitted by the tracers are then measured during respiration by a gamma camera that is placed behind the patient's chair. The tracer activity is visualized and measured by imaging equipment linked to a computer. The computer then constructs pictures that visualize from 1,200 to 1,500 regions in the lung and identifies any diseased area. The information can also be used to determine whether the problem is linked to air flow or pulmonary blood flow. *(See photos above.)*

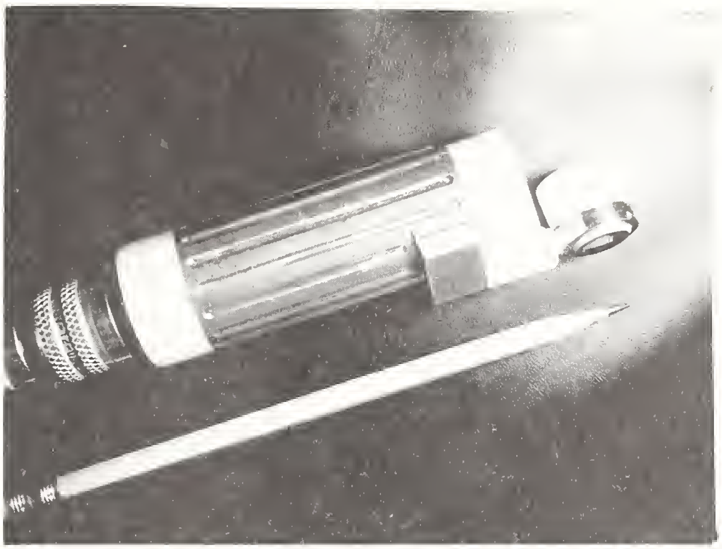
Ultrasound, a different physical technique, utilizes high-frequency sound waves that are reflected by varying tissue densities and shapes revealing the body's internal structure and form.

Ultrasound has two major advantages over X-rays in noninvasive visualization. First, it is capable of visualizing soft tissues without the physician having to resort to injecting "tagged" contrast mediums, which can be hazardous. Secondly, while X-rays are known to cause cellular and tissue damage, ultrasound appears to be safe at the levels of intensity used in the existing equipment. The Diagnostic Radiology Department has made some very real contributions to the technology of ultrasound, many of them as recently as this year.

The first generation of ultrasound scanners were somewhat awkward mechanically. The images they produced were of limited value because vibration and lack of control destroyed much of the image quality.

The second generation devices, called "phased array", used sophisticated electronics to compensate for these earlier drawbacks. While they gave a very good image, their price was quite high, approaching $100,000 per unit.

The mechanically controlled ultrasound scanner developed by Dr. Thomas H. Shawker of Diagnostic Radiology and Mr. William Schuette of the Division of Research Services produces images comparable to the phased-array systems at approximately one-tenth the expense. This is a real-time scanner, which gives a continuous "flouroscopic" image.



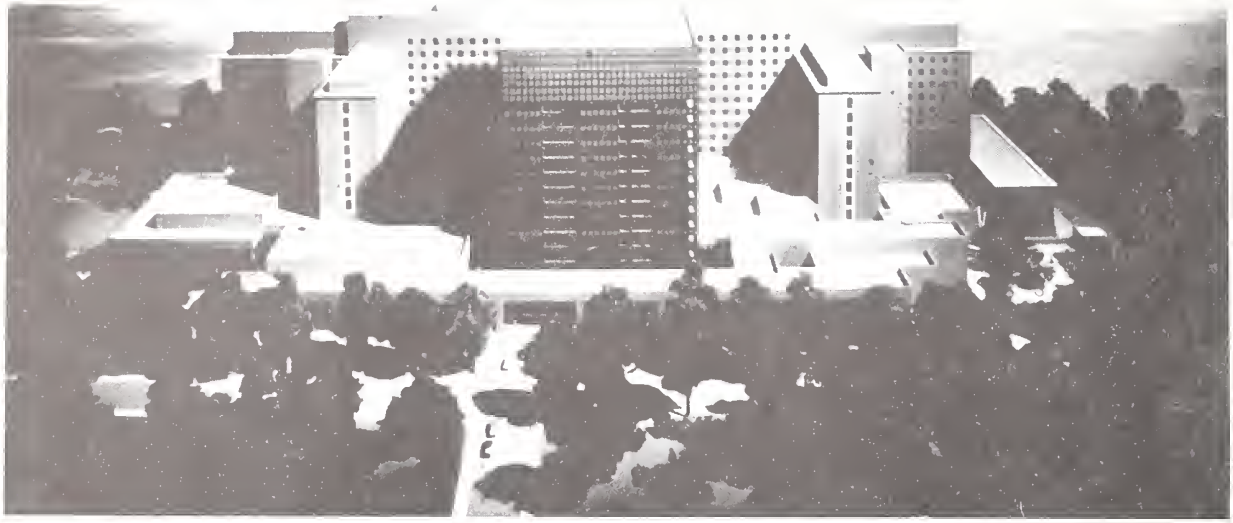
The mechanically-controlled hand-held ultrasound scanner produces images comparable to the electronically-controlled phased-array system at approximately one-tenth of the expense. (NIH Photo #CC-13)

Vibration from the hand-held motor that drives the scanning head was nullified by giving the same motor an equally demanding and necessary task to perform - in the opposite direction - namely to power a position feedback control system. The two torques cancel each other out thus producing zero vibration.

The investigators have been able to further enhance image quality by integrating their scanner to operate "in synch" with television hardware. For many reasons television is the ideal means to both display and store ultrasound-generated images. The Clinical Center researchers use a TV camera to record the position of the scanner on the patient's body on the same videotape that records the ultrasound image, thereby creating a third dimension for diagnostic purposes.

Beyond improving image quality, Dr. Shawker is collaborating with researchers at the National Bureau of Standards to link ultrasound scanners directly with a computer to generate numerical pictures similar to those being used in the CT scanner. The immediate goal is to gain computer-generated quantified measurements. This system could measure the size and volume of a tumor, for instance, before and after chemotherapy. The long-range goal is to perform, via computer-linked ultrasound, an "acoustic biopsy" to find through the proper interpretation on the numerical data not only the volume and location of a tumor, but its particular type, such as melanoma or sarcoma. Establishing such "tissue signatures" will take much additional investigation. The tremendous value of such a system would be the margin of safety that ultrasound has over X-ray - scans could be done repeatedly with no hazard to the patient.

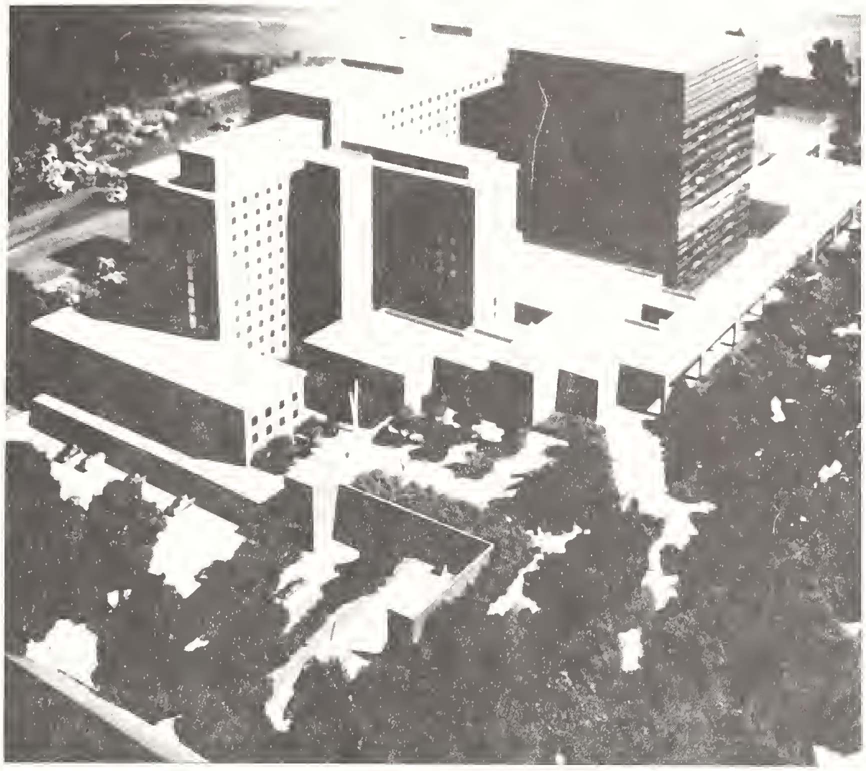
Whether in ultrasound, scintigraphy, angiography, gallium scan, or the refining of new techniques for the CT scanners, the investigators at the Clinical Center are constantly developing new approaches to improve the utility of the diagnostic image.



AMBULATORY CARE RESEARCH FACILITY

A new 13-story Ambulatory Care Research Facility is being constructed to expand and strengthen the combined laboratory and patient care programs of the Clinical Center.

The new facility will provide space for the hospital's rapidly expanding outpatient program. This program, in concert with developments throughout the health care field, is based on achievements during the past few decades that have made it possible to identify many individuals with early stages of disease. Now, many persons with diseases such as cancer, heart disease, and neurological disorders may carry on nearly normal daily lives while being studied and receiving much of their treatment as outpatients.



The Ambulatory Care Research Facility will provide an optimum environment to care for and study outpatients, yet it will retain the same proximity between clinical and basic scientists that has successfully promoted medical inquiry throughout the hospital. Some facilities will be shared with the original building, and all of its inpatient facilities will be available whenever ambulatory patients need them.

When completed in the early 1980's, the new addition to the Clinical Center will accommodate an estimated 300,000 outpatient visits each year, nearly three times the current number. The building will also provide for the expansion of the laboratory research to support the outpatient clinical program.

The Ambulatory Care Research Facility will be built directly in front of the hospital building and will be a 13-floor glass tower on a broad brick base with three underground floors for parking and utilities. Corridors will connect each floor in the tower to the corresponding floor in the existing building so that personnel and supplies may move freely between the two areas.

The base will contain a ground floor lobby, facilities for admitting patients, new quarters for diagnostic radiology and nuclear medicine, a children's area, cafeteria, and public areas. Its second floor will house new operating rooms and clinical pathology laboratories. This part of the facility will accommodate the increased number of patients and at the same time relieve the overcrowding that has occurred during the last few years. It will enable the expansion of medical and surgical intensive care units, modernization and relocation of other services, and renovation of nursing units in the existing building.

CONCLUSION

None of the discoveries reported here, which represent only a tip of the iceberg, would be possible without an ocean of support from each and every Clinical Center department. From the nursing department to the maintenance staff, from the clinical pathology section to the medical records office, from social services to spiritual ministry, each operates under the premise that the highest standards in patient care are inextricably linked with the highest standards in clinical investigation.

Most Clinical Center departments have a research component, even the Fabric Care department is doing investigations in the most efficient manner of cleaning and storing hospital and laboratory linens. All the departments are participating in this most important experiment.

Can two thousand people working together for a single goal - improving the nation's health - make a real difference in the quality of medical care given to the American people?

The preliminary results of the experiment, after the first twenty-five years, are overwhelmingly affirmative.

Editors of publications may request a glossy print of the photographs that appear in this Portfolio.

Mrs. Joyce F. McCarthy
National Institutes of Health
Building 31, Room 2B-10
Bethesda, Maryland 20014

Dear Mrs. McCarthy:

Please send me one glossy print of the photograph from the list below:

CP #1 _____
CP #2 _____
CP #3 _____
CP #4 _____
CC-1 _____
CC-2 _____
CC-3 _____
CC-4 _____
CC-5 _____
CC-6 _____
CC-7 _____
CC-8 _____
CC-9 _____
CC-10 _____
CC-11 _____
CC-12 _____
CC-13 _____

Name: ______________________________

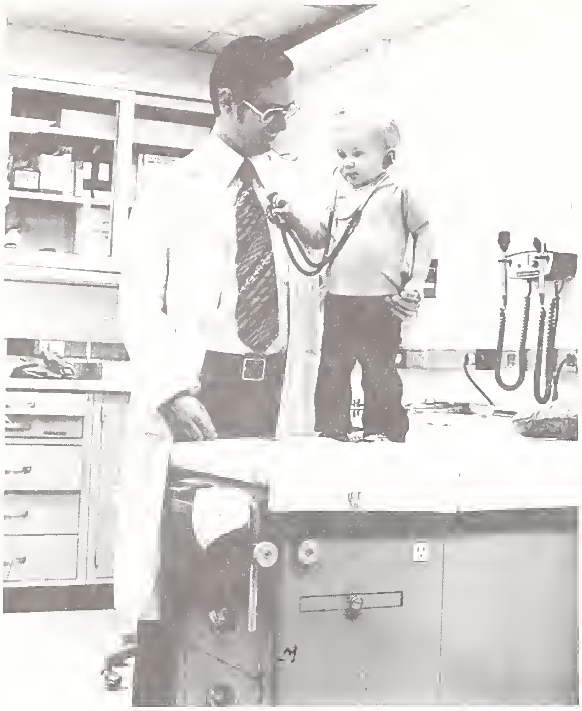
Title: ______________________________

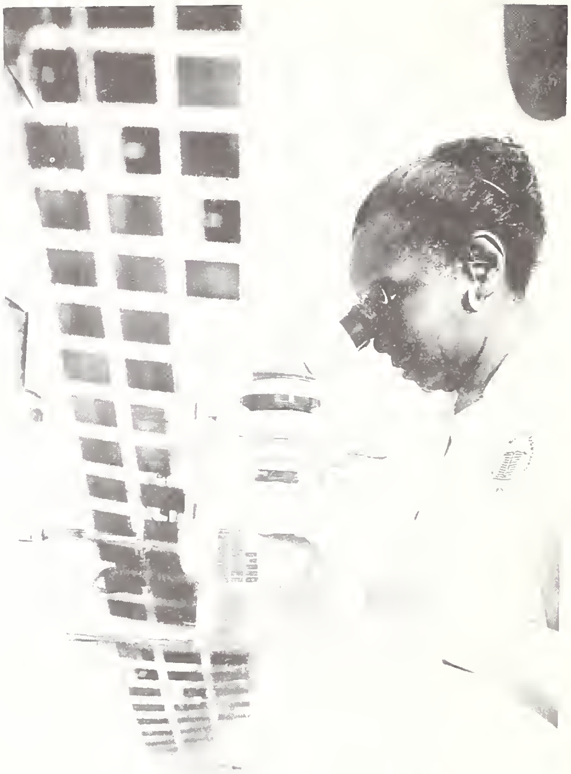
Publication: ________________________

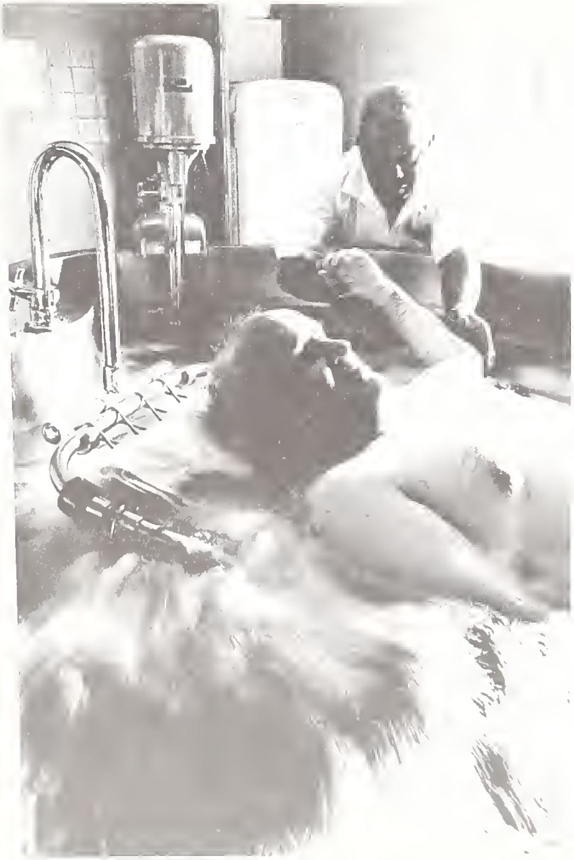
Address: ____________________________

City, State, Zip: ___________________

Telephone: __________________________







NEWS&FEATURES FROM NIH

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE ■ Public Health Service ■ National Institutes of Health ■ Office of Information ■ Bethesda, MD 20205

LIBRARY
JUN 26 1979
NATIONAL INSTITUTES OF HEALTH

June 1979

See page 27

RESEARCH ADVANCES:

Radiation Sensitivity May Be Linked to Hereditary Cancer Tendency..........1
Depression May Be Caused By Metabolic Deficiency..4
Too Much Testosterone May Cause Prostate Gland Enlargement..............8
Chronic Cigarette Smoking Affects Fetal Heartbeat.........11
High Blood Lead Levels Cause Certain Symptoms in Police...14
Chemical Compound Found in Food Causes Cancer in Mice.....19
New Test Developed to Detect Spread of Breast Cancer......21
Insulin Infusion System Normalizes Glucose in Children....23
Intensive Chemotherapy Eliminates Adult Leukemia Cells....25
Atmospheric Pollutants to Be Studied in Air-Tight Chamber.27
Five-Year Clinical Study Initiated for Sickle Cell Disease Patients....................................33
New Primate Publication Available from NIH Division of Research Resources.....................................36

Marc Stern, Editor
Thomas H. Flavin, Associate Editor
NIH News Branch
Building 31, Room 2B-10
Bethesda, MD 20205
Phone: (301) 496-1206

RADIATION SENSITIVITY MAY BE LINKED TO HEREDITARY CANCER TENDENCY

Scientists from NIH's National Cancer Institute and Atomic Energy of Canada Ltd., have found an association between a hereditary tendency to cancer and the sensitivity to radiation of cells from a family with a history of leukemia.

Dr. N.T. Bech-Hansen of Atomic Energy of Canada reported to the annual meeting of The American Association for Cancer Research on May 16, 1979, that skin fibroblasts (connective tissue cells) from four members of a family with a history of acute myelogenous leukemia and reticuloendotheliosis, a form of leukemia, showed increased sensitivity to doses of gamma radiation.

Three of these individuals had cancer, the mother of the family and her two daughters. But cells derived from two cancer-free family members had normal sensitivity, suggesting that only parts of the family had inherited the genes predisposing them to cancer. These studies may provide clues to the mechanisms of leukemia causation, Dr. Bech-Hansen said, as well as add to knowledge of the biological activity of ionizing radiation. The skin cell test also may be of value in predicting an individual's predisposition to leukemia or other cancers.

The family in question is of mixed Irish, English, and American Indian ancestry, and has lived in rural North Carolina for several generations. Segments of the family have lived in separate locations and rarely intermingled. NCI's Dr. John Mulvihill, and others, began studying the family in 1969. Of 35 family members, 7 have developed acute myelogenous leukemia (AML) and 2 suffer from reticuloendothelial cancers.

The scientists found AML and reticuloendotheliosis cases only among

(more)

RADIATION (CONT'D)

maternal relatives, suggesting inheritance by dominant genes according to Mendel's Law of Inheritance. However, the fact that some generations were skipped suggested to the scientists that the predisposition to cancer may require environmental triggers for expression.

Laboratory tests using cells taken from this family have revealed over the years a number of abnormalities which may be associated with the development of leukemia.

Skin fibroblasts grown in the laboratory showed an increased susceptibility to cancerous transformation by the tumor virus SV40. Abnormal levels of immunoglobulins were also found in a number of family members as well as immunological deficiencies associated in other studies with lymphoreticular cancer. Now in these recent experiments, skin fibroblasts from the same and other members of the family appear to have an abnormal sensitivity to radiation.

A high incidence of leukemia has been found in a number of other families in recent years. Scientists believe the best explanation, supported by these experiments, is that some families have a genetically associated sensitivity to ionizing radiation. Other studies also suggest an increased sensitivity to chemicals in the environment might increase sensitivity to radiation.

AML occurs at above average rates in a number of genetic diseases, including Down's syndrome, Fanconi's anemia, and Bloom's syndrome. All these diseases involve chromosome abnormalities. But even where chromosome abnormalities exist, external factors may be required to cause cancer, the scientists said.

That ionizing radiation causes leukemia has been known since studies of

(more)

victims of the Nagasaki and Hiroshima bombings. But the underlying mechanisms are poorly understood. It is not known, for example, whether total body dose of radiation or the dose received by the bone marrow is a more important factor in the causation of leukemia.

Further experiments are now in progress to define the relation between *in vitro* transformation and the development of leukemia, and to determine whether enhanced sensitivity to radiation at the cellular level can be attributed to a defective capacity to repair damaged DNA, the hereditary molecule in the genes of every cell.

###

June 1979

DEPRESSION MAY BE CAUSED BY METABOLIC DEFICIENCY

By Joyce F. McCarthy

Depression may be caused by a specific metabolic deficiency, according to a recent report by researchers at the University of Iowa Psychiatric Hospital and Clinic. Their studies show that depressed patients have uncontrolled development of serum-cortisol, a hormone which increases the ability of cells to make new sugars out of fats and proteins.

Eighty-six patients were tested at the University of Iowa's General Clinical Research Center, which is supported by NIH's Division of Research Resources. To be admitted to the study, the patients had to exhibit the presence of five out of eight possible depressive symptoms with a depressed mood lasting for at least four weeks.

The patients tested were aged 18-85 and diagnosed with having unipolar primary depression, a mental illness characterized by severe withdrawal and uncommunicative behavior, or some form of agitated activity such as hand-wringing, floor-pacing, or talking rapidly about feelings or fears. The controls in the experiment were 80 patients diagnosed as non-depressed, 45 with mania and 35 with schizophrenia.

Before the experiment started, a psychiatric history was obtained by interview from each patient along with a family history. In addition, first-degree family members were interviewed and diagnosed. The 80 controls were diagnosed by the same criteria. Many of the depressed and control patients were receiving some kind of medication for treatment of their mental conditions, and the experiment was conducted for 3-10 days after their admission.

Blood samples were taken from each patient to test their serum-cortisol content. Serum-cortisol is a hormone secreted by the adrenal cortex which

(more)

ncreases the ability of cells to make new sugars out of fats and proteins and egulates the quantity of sugars, fats, and proteins in the blood and cells. he baseline levels of serum-cortisol were found to be slightly higher in the epressive patients.

An overnight dexamethasone suppression test was conducted. Dexamethasone is an anti-inflammatory steroid which is known to accurately gauge endocrine system (hypothalamic-pituitary-adrenal) axis activity. Dexamethasone usually inhibits production of cortisol, but studies have shown that it has no effect on depressives. Depressed patients have shown increased frequency and magnitude of cortisol secretory episodes and increased amounts of cortisol secretions. Increased activity of the hypothalamic-pituitary-adrenal axis (H.P.A.-axis) has been found in a substantial proportion of patients with primary depression. Studies have also found uneven daily secretions of cortisol in depressives.

At the same time the patients were administered the 1 mg. of dexamethasone. Some also received 30 mg. of flurazepam, a short-acting hypnotic. All patients fasted until early the next morning. A third blood sample was then obtained to test the serum-cortisol content, based on the content of serum-cortisol found in the blood after fasting and the administration of dexamethasone.

The results showed that 43 percent (37 out of 86) of the patients diagnosed with unipolar primary depression did not suppress serum-cortisol by dexamethasone. This was not found in any of the 80 controls. The non-suppression of serum-cortisol by the depressive patients did not correlate with sex, age, duration of symptoms, precipitating events, suicide attempt, weight-loss, depression

(more)

test scores, or length of stay in the hospital.

Non-suppression of serum-cortisol distinguished three homogenous genetically defined subtypes of those patients diagnosed with unipolar primary depression. The three subtypes were further distinguished by age of onset and by the number of previous depressive episodes. The findings suggest that unipolar primary depressive illness is three or more separate illnesses, each with a potentially distinctive mode of inheritance, pathophysiology, neurochemistry, clinical course and treatment response.

The three subtypes were distributed as follows: the first, *familial pure depressive disease* (F.P.D.D.),showed 82 percent non-suppression (23 out of 28). F.P.D.D. is simple depression in an individual who has a first-degree relative with depression but no first-degree relative with mania, alcoholism or antisocial personality disorder. The mean age of onset is 33.4 years with more previous episodes of depression. The second, *sporadic depressive disease* (S.D.D.), showed 37 percent non-suppression (13 out of 35). S.D.D. is simple depression in an individual who has no first-degree relative with psychiatric illness. The mean age of onset is 41.3 years. And the third, *depression spectrum disease* (D.S.D.),showed 4 percent non-suppression (1 out of 23). D.S.D. is simple depression in an individual who has a first-degree relative with alcoholism and/or antisocial personality disorder, and who may or may not have a first-degree relative with depression. The mean age of onset is 34.6 years.

These differences were highly significant even though the three subtypes have been found to be symptomatically indistinguishable. Studies done on families and twins suggest that unipolar primary depression is genetic. The

(more)

non-suppressors as a whole were found to have had more depressive episodes and 75 percent of the depressives with a family history of depression were non-suppressors.

Neuropharmacological studies have shown that noradrenaline exerts an inhibiting reaction on the H.P.A.-axis. Theories suggest that a deficiency of noradrenaline in the limbic system may cause depression. This deficiency may concurrently effect the H.P.A.-axis by non-inhibiting it. This results in the H.P.A.-axis left uncontrolled and overactive which in turn causes the resistance to serum-cortisol suppression by dexamethasone.

In any event, there is some common neurophysiological disturbance which may cause both depression and the observed H.P.A.-axis overactivity in the depressive patients. This pathophysiology could be specific to a distinct subtype of depressive illness.

This research was done by Michael A. Schlesser, George Winokur, and Barr M. Sherman from the Departments of Psychiatry and Internal Medicine, University of Iowa College of Medicine, and appeared in the April 7, 1979 issue of the *Lancet*.

###

TOO MUCH TESTOSTERONE MAY CAUSE PROSTATE GLAND ENLARGEMENT

One of the most common medical problems in men over 60 years of age is non-cancerous enlargement of the prostate gland. Because the prostate encircles the urethra where it exits the bladder, when the gland increases in size--as it does in virtually all older men--it often obstructs the flow of urine, thus making it impossible to completely empty the bladder.

The condition, which is termed "benign prostatic hyperplasia" or BPH, produces discomfort and significantly decreases the quality of life for a large number of older men. In fact, in about 75 percent of men who reach the age of 75 the prostate growth results in symptoms of urethral obstruction, which include lack of bladder control, increased urinary frequency and urgency, excessive urination at night and prolonged retention of urine that can lead to urinary tract infection and even kidney failure.

In the past the cause of BPH was unknown. But now a team of researchers at the University of Texas Southwestern Medical School at Dallas has demonstrated that at least in the dog, BPH is caused by an accumulation of "dihydrotestosterone," a form of the principal male hormone testosterone. The scientists presented their findings May 7 in Washington, D.C., at the annual meeting of the American Federation for Clinical Research.

Besides man, the dog is the only mammal that suffers from BPH. (In males of the other mammalian species, prostate glands reach a certain size and then stop growing.) Dr. Jean D. Wilson, professor of internal medicine and director of the McDermott Center for Human Growth and Development at the Dallas medical school, heads the research team. He is quick to point out that their findings in the dog may not be entirely applicable to humans.

(more)

"It's possible, but not proven, that this pathogenic sequence we have worked out in the dog may also apply to humans," Wilson says, "but it will be a long time before it is clear whether these findings have therapeutic implications for men."

There is already a highly effective surgical treatment for BPH, but some older men are poor surgical candidates because they have heart disease or other health problems. In these patients an effective drug therapy would be very useful.

Until now, most of the experimental drugs used to treat BPH have caused "chemical castration" by inhibiting testosterone formation in the testes or its action in the peripheral tissues, Wilson says. (In the 19th Century, surgical castration was the treatment for this condition, he adds.)

The Dallas research team's findings open up several new therapeutic avenues that Dr. Wilson and others are currently exploring. "It may be possible to inhibit the conversion of testosterone to dihydrotestosterone and thus prevent BPH without decreasing the sex hormone level, "Dr. Wilson explains. "Another approach is to attempt to regulate the dihydrotestosterone receptor in the prostate."

"Although surgery will certainly continue to be the treatment of choice for years to come, there are reasons to look for an effective drug therapy," he concludes.

This study is supported by a grant from NIH's National Institute on Aging. The other participants were Dr. John Gazak, formerly a post-doctoral fellow in

(more)

PROSTATE GLAND (CONT'D)

Dr. Wilson's lab and now a urology resident; Dr. Ronald Moore, an assistant professor of internal medicine at UT Southwestern; and James Quebbeman, formerly a research associate in the department of internal medicine.

###

CHRONIC CIGARETTE SMOKING AFFECTS FETAL HEARTBEAT

Chronic cigarette smoking and the effects of nicotine during late pregnancy may be responsible for increased fetal heart rates and possible reduced oxygen supply to the unborn babies.

Researchers in the Department of Reproductive Medicine at the University of California, San Diego, studied 8 women volunteers who habitually smoked 20-40 cigarettes per day and were 8½ months pregnant. The patients were recruited from the University of California's General Clinical Research Center (GCRC).

The patients were studied at the GCRC where they were placed at bed rest and remained so throughout the study. Blood pressure and pulse recorders were attached to the patients' arms and external fetal heart monitors were applied to the abdomen for continuous recording of fetal heart rates.

Three blood samples were taken at 10 minute intervals from each patient before the experiment began. The patients started the experiment with a period of sham smoking using an 8.5 cm (about 3½ inches) section of a drinking straw. Blood samples were then drawn at timed intervals and recorded. The patients then smoked two standard nonfiltered 8.5 cm cigarettes in 10 minutes. Blood samples during cigarette smoking were obtained at the same time intervals as during sham smoking with additional samples taken at 40, 50, and 60 minutes after the mothers started smoking. Maternal pulse rate and blood pressure were recorded at 2½ minute intervals and fetal heart rates were monitored continuously throughout the study.

The blood sample results showed cigarette smoking, but not sham smoking, induced rapid and significant elevations of maternal pulse, blood pressure and carbon monoxide concentrations. Maternal blood pressure began to rise signifi-

(more)

KING (CONT'D)

ntly 2½ to 5 minutes after smoking. Carbon monoxide concentrations began rise, but were not significant until 5 minutes after smoking. Significant anges in norepinephrine and epinephrine occurred within 2½ minutes after the thers started smoking, but the dopamine level did not change significantly. orepinephrine, epinephrine and dopamine are all plasma catecholamines -- complex emical substances derived from an amino acid whose actions resemble sympathetic rve impulses and cause stimulation of blood pressure, metabolic rate, and art rate).

During the first 7½ minutes of smoking, fetal heart rates increased gnificantly. A peak increase occurred 17½ minutes after the mother started oking, which eventually returned to normal levels along with catecholamine vels, but the maternal carbon monoxide concentration still increased.

Studies done on experimental animals indicate that nicotine crosses the lacenta rapidly which it also appears to do in humans. The nicotine component f cigarette inhalation appears responsible for the rapid catecholamine release nd peripheral blood vessel constriction in the mother. The onset of fetal eart rate changes within minutes of maternal catecholamine changes is consistent ith fetal oxygen deprivation and probably due to reduced blood flow in the womb. possible explanation of increased fetal heart rates could be attributed to tress caused by uteroplacental constriction.

In summary, these findings indicate that chronic cigarette smoking during ate pregnancy results in acute changes in maternal neuroendocrine and cardioascular functions which affect a chronic decrease in oxygen tension and blood low from the mother to the unborn child. Nicotine, along with an increased

(more)

inhalation of carbon monoxide may be direct contributors to increased fetal heart rates and could result in low-birth weight infants and other complications.

This research was supported in part by the NIH's Division of Research Resources, the National Foundation March of Dimes, and the Rockefeller Foundation. M.E. Quigley, K.L. Sheehan, M.M. Wilkes, and Dr. S.S. Yen reported their research in the March 15, 1979 issue of *American Journal of Obstetrics and Gynecology*.

###

June 1979

EWS & FEATURES From NIH

HIGH BLOOD LEAD LEVELS CAUSE CERTAIN SYMPTOMS IN POLICE

By Dinah M. Bertran

A study of law enforcement officers, particularly firearms instructors, has found a higher prevalence of elevated blood lead levels and central nervous system symptoms.

Researchers at the Mt. Sinai School of Medicine, supported in part by NIH's National Institute of Environmental Health Sciences, have recently published a paper entitled, "Exposure to Lead in Firing Ranges", detailing the examination of 81 New York City policemen for blood lead levels and for symptoms relating to lead poisoning. The study also assessed the physical conditions at three indoor firing ranges to see whether they adhered to occupational safety recommendations for minimal exposure to lead particulates in the air.

Because law enforcement officers have to be proficient with handguns, indoor firing ranges are increasingly used for regular training programs. In addition, handguns are becoming more popular for recreation by the general public. Indoor firing ranges pose a distinct threat to lead absorption due to the amount of lead getting into the air. Lead is absorbed in two forms; as elemental lead and as lead oxide. Particles of lead are released by friction of the bullets against the gun barrels and by breaking up of bullets hitting the target or backstop. Guns also produce lead fumes (lead oxide) by combustion of lead in priming compounds. Other harmful chemicals are also released into the air from combustion of ammunition. The type and amount of ventilation at indoor firing ranges is extremely important, yet many ranges tested by the National Institute for Occupational Safety and Health were found not to have proper ventilation to keep lead levels below the standard ($50\,\mu g/M^3$)

(more)

LEAD (CONT'D)

There are many symptoms of lead intoxication. Lead can affect the central nervous system, causing hyperirritability, headache, nervousness, dizziness, fatigue, weakness, and both inability to sleep (insomnia) and uncontrollable sleepiness (somnolence). It also can cause gastrointestinal symptoms including loss of appetite (anorexia), nausea, weight loss, and stomach pain. In addition, there can be muscle and joint pain and muscle weakness.

The police officers were questioned about symptoms possibly related to lead toxicity, and both medical and occupational histories were taken. The researchers were also interested in identifying those officers with a longer length of employment, and therefore probably a longer overall period of time spent on firing ranges.

All 81 men were tested for both blood lead levels and zinc protoporphyrin (ZPP) concentrations. Blood lead levels were tested by passing blood samples through an atomic absorption spectrophotometer, which measures lead content by variations in flame color and brightness. The lead is recorded in µg/dL (micrograms per deciliter). Less than 40 µg/dL is considered acceptable, anything above being suspect. It is generally considered to be extremely serious when the level goes to 60 µg or above.

Zinc protoporphyrin (ZPP) concentrations were determined by using a portable hematofluorometer. ZPP is a substance present in small amounts in human red blood cells. It is thought that the lead present in the red blood cells causes ZPP to form an abnormal hemoglobin, which is fluorescent. The degree of fluorescence monitored indicates the amount of ZPP incorporated

(more)

into the hemoglobin.

Since the life of a red blood cell is about four months, ZPP determinations offer an indication of cumulative exposure to lead rather than blood lead levels, which measure recent and current exposure to lead.

Lead concentrations in the air at the firing ranges were also tested using atomic absorption spectrophotometry. Air samples were collected on small filters, which, after preparations, were run in the spectrophotometer. Amounts of lead in the air were determined before firing and during firing at both the firing booths and the instructor stations.

Of the 81 law enforcement personnel tested, 43 were full time firearms instructors. Twenty-three of the 81 policemen were tested twice; the first screening was immediately after a four-month outdoor training period, and the second screening immediately followed a four-month indoor training period.

The initial screening of the 81 officers showed a relationship between blood lead levels and reported central nervous system (CNS) symptoms. The higher the amount of lead in the blood and also the higher the ZPP determinations, the greater the number of those officers reporting CNS symptoms. In addition, more than half (52 percent) of the officers had blood lead levels higher than the acceptable 40 µg/dL; 14 percent of these had levels between 50 and 59 µg/dL; 5 percent had levels exceeding 60 µg/dL; and one had a level of 87 µg/dL. More striking is the fact that at the second screening (which immediately followed the indoor training period), the blood lead levels of seven out of twenty-three individuals tested were elevated significantly. At the second screening, these seven persons had blood levels above the cut-

(more)

off level of 40 ug/dL; whereas, prior to indoor training, their levels had been below 40 ug/dL. ZPP determinations were also high for the initial screening, and were further raised at the second screening of those officers tested twice.

One of every four of the officers reported CNS symptoms. Furthermore, those who had been employed longer were more likely to have reportable symptoms. Yet persons with shorter lengths of employment (one to five years) still reported symptoms frequently--slightly over one in every five officers. Seventy-five percent of the officers with blood lead levels over 60 ug/dL reported CNS symptoms, as did 62 percent of those with elevated ZPP.

Gastrointestinal symptoms also increased with longer length of employment and elevated blood lead levels.

Especially striking is the fact that six officers reported both CNS and gastrointestinal symptoms, and that of these six, five were full time firearms instructors. In addition, among these five there was a median blood lead level of 63 ug/dL, and also a high ZPP level. They also had a longer length of employment.

Concentration of lead in the air at three New York City indoor firing ranges was tested. Two ranges had an unsafe amount of lead in the air due to improper ventilation systems; the air was not directed away from the breathing area and there was not enough air being exhausted from the ranges. Ventilation at one of the three ranges fell within the standards of the Occupational Safety and Health Administration.

The authors concluded that lead related symptoms, especially those of the

(more)

central nervous system and gastrointestinal tract, may occur frequently among firearms instructors. To minimize lead disease, Dr. Alf Fischbein, the principle investigator, and his colleagues recommended that firing ranges adhere to currently recommended design criteria. They also recommended the regular medical monitoring of firearms instructors for blood lead levels, ZPP determinations, and symptoms associated with lead toxicity.

The findings were published in the March 16 issue of the *Journal of the American Medical Association.*

Co-investigators in the study included Irving Selikoff, M.D., of the Mt. Sinai Environmental Sciences Laboratory, and Clarence G. Robinson, M.D., chief police surgeon of the New York City Police Department.

###

June 1979

NEWS & FEATURES From NIH

CHEMICAL COMPOUND FOUND IN FOOD CAUSES CANCER IN MICE

A chemical compound made up of two components present in the food we eat has been found to cause cancer when given orally to mice. The compound, N^6-(Methylnitroso)adenosine, called m^6(NO)Ado for short, is the product of the combination of sodium nitrate, a commonly-used food preservative, and N^6-methyladenosine, an amine that is present in minute amounts in foods and most living cells.

Speaking at a meeting of the American Association of Cancer Research on May 16, 1979, Dr. Alfredo Giner-Sorolla of the Sloan-Kettering Institute for Cancer Research of New York presented the results of a study in which he and Dr. Lucy M. Anderson gave mice a dilution of the compound in their drinking water. The mice developed many lung and reproductive tissue tumors.

In an earlier study, Drs. Giner-Sorolla and Anderson showed that the same compound, injected into the peritoneum (the space surrounding the abdominal organs) of mice caused lung, lymphoid and liver cancers. This new study has shown that when the compound was taken by mouth, which is how humans would experience it, a high incidence of tumors again occur in the mice.

Another finding was that female mice who received the compound orally developed many tumors in the reproductive organs.

The orally-administered compound resulted in lung tumors in 63 percent of the males and 80 percent of the females. Only 19 percent of the control animals developed malignant lung tumors. Eighty percent of the females exposed to the compound also had tumors of the reproductive tissues. Of the exposed group, 55 percent developed mammary cancers, 25 percent malignant uterine tumors, and five percent ovarian cancers.

(more)

FOOD (CONT'D)

The percentages of tumor incidence in the study were high because the mice were given large doses of the compound to accelerate its effects. These doses are not necessarily equivalent to those experienced by most humans. It is common practice to give large doses in laboratory tests for carcinogenicity, because the number of animals that can be used is limited and drugs that would affect only a small number of humans out of the general population would otherwise go unnoticed.

When the two components of the compound (sodium nitrite and N^6-methyladenosine) were given singly to control groups of mice, they did not cause tumors. When both components were given at the same time to a group of mice, the mice had the same incidence of lung tumors (61 percent) as the group receiving the m^6(NO)Ado compound.

The scientists theorize that the two components of m^6(NO)Ado are chemically combined under the conditions of the digestive tract into the cancer-causing compound.

Researchers must now determine whether this intra-gastric chemistry actually does occur, and if it does, determine whether enough of this carcinogen is formed from the food we eat to be a likely cause of certain cancers in humans.

The research was partially supported by grants from NIH's National Cancer Institute.

###

NEW TEST DEVELOPED TO DETECT SPREAD OF BREAST CANCER

Investigators at the National Institutes of Health report progress toward developing a diagnostic test that ultimately may help pathologists diagnose the spread of even a few cancer cells from the breast to adjacent lymph nodes. With present methods, differentiating between metastatic and inflamed cells in lymph nodes sometimes is difficult.

The new method, being tested by investigators at the National Institute of Dental Research and the National Cancer Institute, also may prove useful in determining the source of other types of undifferentiated tumors because the technique selects out cells of epithelial origin such as breast tumor cells, and not cells originating from mesenchyma. New tools are needed to determine whether undifferentiated tumors (whether primary or metastatic) are of epithelial or connective tissue origin because treatment differs for various kinds of cancer.

Knowledge gained by NIDR scientists doing research on collagen, the chief connective tissue protein in the body, is the basis for the new method. NIDR scientists are studying collagen because it is the principal protein of mineralized tissues, it holds teeth in the jawbone, and it plays a role in wound healing and in craniofacial development.

The investigators first performed basic research to identify and purify the several types of collagen. After purifying type IV, basement membrane collagen, which is made by breast and by other epithelial cells, they obtained antibodies to the collagen by immunizing rabbits with the protein.

When cells are coated with this type of antibody, only normal and cancerous epithelial cells fluoresce or are stained by it. The NIDR team is continuing to

(more)

collaborate with Dr. Lance A. Liotta, an NCI investigator, to see if the purified antibodies to type IV collagen can be used to distinguish cancer cells of epithelial origin from tumor cells not of epithelial origin (fibrosarcomas and lymphomas, for example). Preliminary evidence suggests that the new method will localize epithelial cells because only those cells synthesize detectable levels of type IV collagen.

When tissue specimens taken from patients who underwent diagnostic breast biopsies or mastectomies were stained with antibodies to basement membrane collagen, all 16 breast carcinomas studied stained positively for the presence of the basement membrane, type IV collagen. Dr. Jean-Michel Foidart, a Visiting Associate at the NIDR, said "all 16 specimens stained to antibody to type IV collagen. Tissues usually fluoresced in the cytoplasm but occasionally fluorescence occurred extracellularly. Breast cancer *in situ* stained prominently; in lymph node metastases, individual tumor cells or small clusters of such cells could be distinguished clearly from surrounding lymphoid cells."

In contrast, inflammatory cells and macrophages in the lymph nodes which resemble transformed (cancerous) cells are not stained by the antibody. Therefore, the antibody staining technique may prove useful in diagnosing the spread of breast cancer. Further, breast cancer cells stain only when treated with the type IV collagen antibodies and not when coated with other substances (such as rabbit anti-type I collagen antibodies, normal rabbit serum, normal goat serum, rabbit anti-ovalbumin antibodies and rabbit anti-human IGG, IGM Kappa and Lambda chain antibodies.)

###

NEWS & FEATURES From NIH June 1979

INSULIN INFUSION SYSTEM NORMALIZES GLUCOSE IN CHILDREN

Prolonged plasma glucose normalization, resulting from treatment with a portable insulin infusion system, was observed in eight juvenile onset diabetics in a two-week study conducted by the Yale School of Medicine research scientists who developed the treatment. The study is part of their continuing research to determine the long-term efficacy of the system, which functions as an artificial pancreas.

At the annual meeting of the American Federation for Clinical Research in Washington, D.C., in May, 1979, Dr. Philip Felig, senior investigator of the study, reported that none of the patients, who were 16 to 26 years of age and fully ambulatory, experienced symptoms of hypoglycemia during the two-week period. The study also revealed that in addition to its affect on plasma glucose, the insulin infusion system normalized other nutrients as well, particularly protein metabolism. The investigators, Drs. William Tamborlane, Robert Sherwin, Myron Genel and Felig, noted that further studies of the prolonged use of this treatment may resolve questions of the role of hyperglycemia in diabetic complications such as kidney failure, loss of vision, and peripheral vessel disease.

The system differs from previous attempts to control diabetes with an artificial pancreas in that it does not require insertion of a needle or tube in a vein, which could lead to infection of thrombosis (blood clotting). It consists of a commercially available battery driven insulin pump, which is attached to the patient by a belt, and is programmed manually to infuse insulin throughout the day and night in predetermined dosages. A small plastic tube carries the insulin from the pump to a minute needle inserted

(more)

under the skin of the abdomen.

The study was funded in part by NIH's Division of Research Resources, and NIH's National Institute of Arthritis, Metabolism and Digestive Diseases. It is a joint project of the Department of Medicine and the Department of Pediatrics at the Yale School of Medicine.

###

NEWS & FEATURES From NIH

June 1979

INTENSIVE CHEMOTHERAPY ELIMINATES ADULT LEUKEMIA CELLS

An intensive chemotherapy treatment developed at Memorial Hospital for Cancer and Allied Diseases in New York has resulted in the complete disappearance of abnormal blood cells peculiar to an adult leukemia known as chronic myelogenous leukemia or CML. The cells, which have a characteristic chromosome abnormality named the "Philadelphia chromosome," have been temporarily eliminated in a small group of patients by an experimental treatment known as the L-15 protocol.

Dr. Zalmen Arlin, assistant attending physician on the Hematology-Lymphoma Service at Memorial, described attempts to destroy cells with the Philadelphia chromosome abnormality at a meeting of the American Society of Clinical Oncology in New Orleans on May 14.

Eliminating these cells is vital if CML patients are to be cured, because a single remaining cell can generate a new wave of Philadelphia-positive cells and cause a recurrance of the disease.

In a treatment trial using the L-15 protocol, a combination of anticancer drugs, Philadelphia-positive cells disappeared in nine of fifteen patients. Four of these patients remain free of the cells from four to nineteen months after treatment.

Researchers think the Philadelphia chromosome defect is the mark of an acquired abnormality (the cause of which is not known) which stems from a single ancestral cell common to both red and white blood cells. Although the descendents of this cell are leukemic, they can function somewhat normally for a period. But ultimately, in most instances the disease takes on the characteristics of acute leukemia. The patients die from acute infection, severe

(more)

CHEMOTHERAPY (CONT'D)

anemia, or hemorrhage.

Memorial clinical researchers hope to be able to kill off the positive cells at least long enough to get a supply of the patients own blood-producing bone marrow in a disease-free state. Then, pure Philadelphia-negative cells would be isolated from the marrow - by techniques yet to be devised - and saved. After the patients receive intensive chemotherapy to destroy any residual Philadelphia-positive cells, the saved marrow could be given back to patients to reconstitute their blood with their own healthy cells.

Co-researchers in the L-15 study were Sanford Kempin, M.D., Timothy Gee, M.D., Tatsuhiko Goto, Raju Chaganti, Ph.D., Elisa Koenigsberg, Joseph Burchenal, M.D., and Bayard Clarkson, M.D.

The research was partially supported by NIH's National Cancer Institute.

###

NEWS & FEATURES From NIH
June 1979

ATMOSPHERIC POLLUTANTS TO BE STUDIED IN AIR-TIGHT CHAMBER

University of Rochester Medical Center researchers have demonstrated a unique environmental chamber in which they will start controlled studies on the effects of typical atmospheric pollutants--including automobile exhaust components--on the human respiratory system.

The new 300-square-foot air-tight chamber is part of the medical center's General Clinical Research Center, a special eight-bed unit located in the University's Strong Memorial Hospital and devoted exclusively to clinical (human) research purposes. The University of Rochester Clinical Research Center is one of 75 such units funded by NIH's Division of Research Resources, and located at select medical centers throughout the United States, according to Dr. Richard Hyde and Dr. Paul Morrow, who are in charge of the research team.

Dr. Morrow explained that past research which studied the effects of environmental pollutants on humans was limited in scope because it usually involved only normal or healthy research participants who were exposed to high levels of pollutants for short periods of time. Often, these studies utilized mouthpiece connections for pollution exposure thereby totally disregarding the nasal airways. According to Dr. Morrow, these short-term studies also did not cope with normal living situations, changes in daily activity patterns, and long-term cumulative effects.

The new aerosol chamber will allow the University of Rochester researchers to avoid these constraints by designing studies of longer duration with the research participants exposed to normal levels of pollution in an environment where they can simulate normal living situations. The studies also will

(more)

involve research participants with respiratory disorders, as well as normal or healthy participants.

"People with respiratory diseases make up a large and significant portion of the population, "Dr. Hyde explains. "Therefore, if we are to take a complete look at this problem, it seems they should be included in the research effort."

In order to simulate normal physical activity, the research participants will perform intermittent light exercise on a bicycle ergometer which will be in the chamber. Dr. Hyde said the researchers will measure pulmonary function parameters as well as oxygen consumption during and after the exercise period. In addition, the participants' physiological status can be monitored frequently by equipment in the chamber and through the laboratory facilities of the General Clinical Research Center.

"The development of the chamber within the Clinical Research Center means that specimen collection can be carried out by a well-trained staff familiar with sophisticated research procedures and that these specimens can be analyzed quickly in the hospital and Clinical Research Center laboratories," Dr. Hyde explains. In short, we will have access to routine hematology, chemistry, and urine studies, as well as continuous sophisticated nursing support."

Dr. Thomas G. Bowery, director of NIH's Division of Research Resources, said the University of Rochester environmental pollutant studies will be the first time that research of this design has been undertaken within the setting of a Clinical Research Center.

The environmental chamber was designed and constructed from a normal

(more)

General Clinical Research Center hospital room, according to Dr. Laurence Jacobs, director of the Center. The pollutants will be released into the chamber through a specially designed ventilation system. The room air-turnover can be modified by controlling the ventilation input. Researchers will be able to control the temperature and humidity within the chamber. The chamber will include a living area with two beds, two chairs, and a night-stand; an adjoining bathroom; and an antechamber which will remain free of the aerosol pollutants and contain monitoring equipment and the pollutant generator.

During the initial research project, submicroscopic particles of three sulfate chemicals normally associated with atmospheric pollution, such as automobile exhaust fumes, will be released into the chamber in aerosol form through the room's specially designed air ventilation system. The aerosols to be studied--sodium sulfate, ammonium sulfate, and sulfuric acid--will be released in quantities normally found in many American urban environments.

Normal, healthy research participants will be studied first, according to Dr. Hyde. The initial participants will be laboratory personnel and volunteers from the University of Rochester.

If no or minimal effects are found in these first normal participants, the study will then extend to both asthmatics and participants with other forms of lung disease. These volunteers also will be recruited from the University population and hospital clinics.

In the early phases of the research, the investigators will study the effects of several four to six-hour exposures during a three-day period. If

(more)

POLLUTANTS (CONT'D)

minimal effects are found on the participants during these short term exposures, the researchers then plan on extending the exposures to a 24-hour period.

Dr. Hyde explains the value of the research: "Currently there is inconclusive information about many agents in atmospheric pollution which may be responsible for adverse human health effects. Studies in normal animals seem to indicate there is little problem with automobile exhaust, but epidemiological studies would indicate otherwise. Although some human research evidence tends to suggest that certain pollutants and particulate matter are more damaging to health than others, opinions continue to change and uncertainties prevail.

"The most significant potential result of studies done in the new environmental chamber will be to identify causative agents, or at least to place these agents in a far more definitive status than possible in the past.

"A second potential benefit would relate to the differences found in normal participants and those with lung diseases such as asthma and emphysema. This will provide a basis for estimating risks and establishing safety factors with any proposed pollution standard.

"Hopefully, we can then begin to answer questions such as: Which pollutants are causing reactions? Which pollutants are causing reactions in certain individuals? What role does temperature and humidity play in the effect of pollutants?

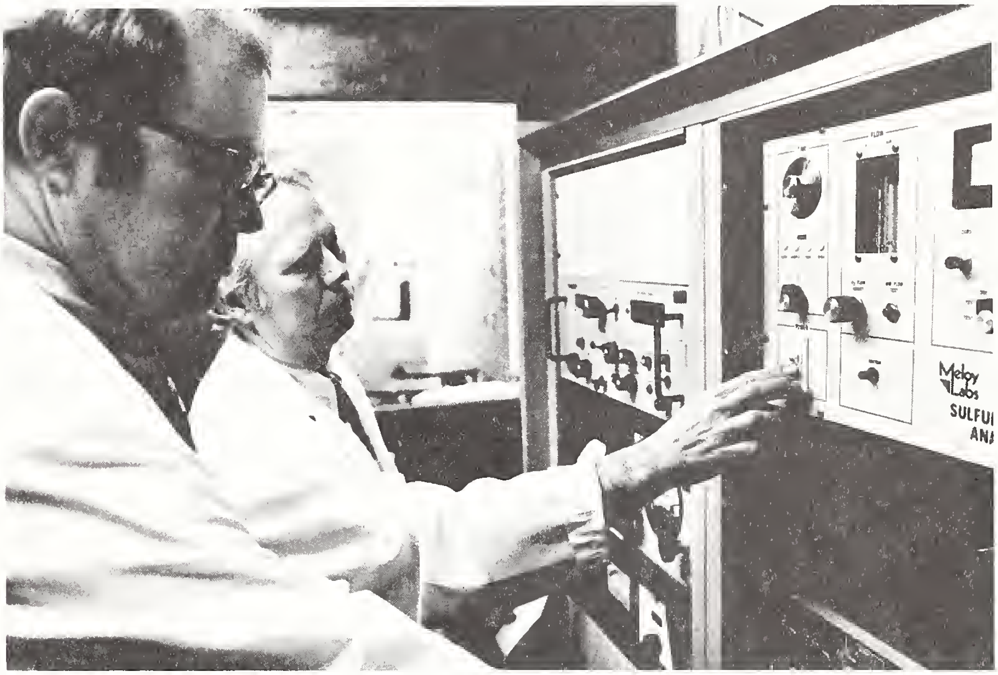
"The answers to these questions can possibly provide guidance in manufacturing motor vehicles which can better control damaging pollutants and in

(more)

POLLUTANTS (CONT'D)

developing more meaningful legislation."

Working with Dr. Hyde and Dr. Morrow are members of the Pulmonary Disease Unit of the Department of Medicine and the Aerosol Physiology Team in the Department of Radiation Biology and Biophysics.



Dr. Richard Hyde (left) and Dr. Paul Morrow of the University of Rochester Medical Center carefully check readings indicating conditions inside the University's new Environmental Pollutant Chamber. The chamber, which will help researchers determine the effects of various atmospheric pollutants on the human respiratory system, is located on the medical center's General Clinical Research Center, a special unit for clinical research purposes funded by the Division of Research Resources, National Institute of Health.
(NIH Photo #1622)

(more)

Atmospheric pollutants will enter the University of Rochester's new airtight Environmental Pollutant Chamber through vents in the ceiling of the recently converted hospital room. Researchers will use the chamber to determine the effects of atmospheric pollutants on the human respiratory system. The facility is located on the medical center's General Clinical Research Center, a special unit for clinical research funded by the Division of Research Resources, National Institutes of Health. (NIH Photo #1623)

###

NEWS & FEATURES From NIH

June 1979

FIVE-YEAR CLINICAL STUDY INITIATED FOR SICKLE CELL DISEASE

The Sickle Cell Disease Branch, Division of Blood Diseases and Resources of NIH's National Heart, Lung, and Blood Institute, has initiated a five-year comprehensive longitudinal, prospective, cooperative study on the clinical course of sickle cell disease.

The objective of this study is to determine the natural history of sickle cell disease by clinical evaluation of patients diagnosed as having the disease. Although sickle cell anemia and related hemoglobinopathies involving sickle hemoglobin have been recognized for many years and numerous clinical and laboratory manifestations have been described, the clinical course of sickle cell disease is poorly documented. Most of the available data are anecdotal, retrospective and lack statistical validity.

Twenty-three hospitals across the U.S. are participating in the study (list attached). Investigators at these hospitals will recruit 3,500 patients, including newborns, children, adolescents and adults to participate. Data management and coordination will be centralized through the Statistical Coordinating Center at the University of Illinois, Chicago. Patient entry began in March.

For further information regarding participating institutions or any other aspects of this study, please contact:

Marilyn Gaston, M.D.
Sickle Cell Disease Branch
Division of Blood Disease and Resources
NHLBI
Bethesda, MD 20205
(301) 496-6931

(more)

SICKLE CELL (CONT'D)

Bertran Lubin, M.D.
Children's Hospital of Northern California
51st and Groove Streets
Oakland, California 94609
(415) 654-5600

William Mentzer, M.D.
San Francisco General Hospital
1001 Potrero Avenue
San Francisco, California 94110
(415) 821-5169

Howard Pearson, M.D.
Yale University Medical Center
333 Cedar Street
New Haven, Connecticut 06510
(203) 436-0316

Sanford Leikin, M.D.
Children's Hospital Medical Center
111 Michigan Avenue, N.W.
Washington, D.C. 20010
(202) 745-2140

Lawrence Lessin, M.D.
George Washington University Medical Center
2150 Pennsylvania Avenue, N.W.
Washington, D.C. 20037
(202) 676-2939

Roland B. Scott, M.D.
Howard University Center for Sickle Cell Disease
2121 Georgia Avenue, N.W.
Washington, D.C. 20059
(202)636-7930

Donald Harkness, M.D.
University of Miami Medical Center
P.O. Box 520875 - Biscayne Annex
Miami, Florida 33152
(305) 547-6924

Paul Milner, M.D.
Medical College of Georgia
1526 Laney-Walker Boulevard
Augusta, Georgia 30901
(404) 828-3091

Mable Koshy, M.D.
Michael Reese Medical Center
2900 South Ellis Avenue
Chicago, Illinois 60616
(312) 791-2798

Robert Chilcote, M.D.
Wyler Children's Hospital
University of Chicago
5801 South Ellis Avenue
Chicago, Illinois 60637
(312) 947-6308

William Adams, M.D.
Trustees of Health and Hospital
Boston City Hospital
818 Harrison Avenue
Boston, Massachusetts 02118
(617) 424-4034

David Nathan, M.D.
Children's Hospital Medical Center
300 Longwood Avenue
Boston, Massachusetts 02115
(617) 734-6000 Ext-3471

Martin Steinberg, M.D.
University of Mississippi Medical Center
2500 North State Street
Jackson, Mississippi 39216

Harold Zarkowsky, M.D.
St. Louis Children's Hospital
500 South Kings Highway
P.O. Box 14871
St. Louis, Missouri 63110
(314) 367-6880 Ext-371

(more)

SICKLE CELL (CONT'D)

Harvey Dosik, M.D.
Jewish Hospital and Medical Center
Of Brooklyn
555 Prospect Place
Brooklyn, New York 11238
(212) 240-1211

Audrey Brown, M.D.
SUNY Downstate Medical Center
450 Clarkson Avenue
Brooklyn, New York 11203
(212) 270-1692

Arthur Bank, M.D.
The Presbyterian Hospital
Columbia Presbyterian Medical Center
622 West 168th Street
New York, New York 10032
(212)694-6537

Doris L. Wethers, M.D.
St. Luke's Hospital Center
Amsterdam Avenue at 114th Street
New York, New York 10025
(212) 870-1756

Yusuf Khakoo, M.D.
Harlem Hospital Medical Center
135th Street and Lenox Avenue
New York, New York 10037
(212) 694-8074

Wendell F. Rosse, M.D.
Duke University Medical Center
3934M
Durham, North Carolina 27710
(919) 684-4237

Francis Gill, M.D.
Children's Hospital of Philadelphia
34th and Civic Center Boulevard
Philadelphia, Pennsylvania 19104
(215) 596-9873

Judith Wilimas, M.D.
St. Jude Children's Hospital
332 North Lauderdale
P.O. Box 318
Memphis, Tennessee 38101
(901) 525-8381

Alfred P. Kraus, M.D.
University of Tennessee
Comprehensive Sickle Cell Center
800 Madison Avenue
Memphis, Tennessee 38103
(901) 528-5798

Statistical Coordinating Center

Edwin Chen, Ph.D.
University of Illinois Medical Center
School of Public Health
2121 West Taylor
Chicago, Illinois 60612

###

PRIMATE PUBLICATION
ILABLE FROM DRR

The publication, *NIH Primate Research Centers: A Major Scientific Resource,* been totally revised and is available free from NIH's Division of Research ources.

Containing 64 pages and 84 photos, the new booklet describes in detail the tory, principal research emphases, administration, research teams, research ilities, primate colonies, and services of the seven NIH national primate ters which are supported by the Division of Research Resources.

The Primate Research Centers Program of NIH began in 1960. As the largest human primate research center network in the world, the program's main sion is to identify primate models in which diseases can be studied and dup- ated, their causes and effects documented, and effective means of prevention d treatment developed.

The primate research center studies include reproductive biology and popu- tion control, infectious diseases, neural and behavioral research, metabolic d degenerative diseases, cardiovascular diseases, environmental health sciences, d dental research.

The original edition of *NIH Primate Research Centers: A Major Scientific source* was published in December 1971. The 1978 revised edition reflects the anges in emphasis within the individual centers to assure that strong biomedical search programs continue to be focused on important and current problems.

One free copy of *NIH Primate Research Centers: A Major Scientific Resource* y be requested by writing to the Office of Science and Health Reports, Division Research Resources, National Institutes of Health, Bethesda, MD 20205.

###

Editors of publications may request a glossy print of the numbered photographs that appear in this issue.

Ms. Maureen Napper
National Institutes of Health
Building 31, Rm. 2B-10
Bethesda, Maryland 20205

Dear Ms. Napper:

Please send me one glossy print of the numbered photographs checked below:

1622 _____

1623 _____

Name: ______________________________

Title: ______________________________

Publication: ________________________

Address: ___________________________

City, State, Zip: ___________________

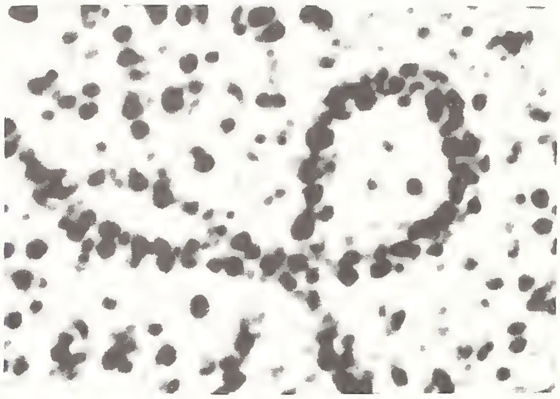
Telephone: _________________________

NEWS&FEATURES FROM NIH

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE ▪ Public Health Service ▪ National Institutes of Health ▪ Office of Information ▪ Bethesda, MD 20205

LIBRARY
MAR 22 1979
NATIONAL INSTITUTES OF HEALTH

March 1979



See page 7

RESEARCH ADVANCES:

Study Finds Less Risk of Cancer in Daughters of DES-Exposed Mothers.....1
Natural Gene Clones Yield New Clues to the Role of Intervening DNA Sequences...............7
Diabetes Genes Protect "Thrifty" Mice from Starvation.....17
US-USSR Begin Collaborative Research in Eye Diseases......20
Decline in Fat Metabolism May Be Cause of Shortened Life..22
Antibiotic Resistance Can Transfer in Mouth...............24
Oral Contraceptives May Not Cause Birth Defects...........27
Initial DNA Risk Assessment Studies Find Infection Hazard Minimal..29

In Perspective: Rabies Transmitted Through Corneal Transplant...34

Marc Stern, Editor
Thomas H. Flavin, Associate Editor
NIH News Branch
Building 31, Room 2B-10
Bethesda, MD 20205
Phone: (301) 496-1206

NEWS & FEATURES From NIH March 1979

STUDY FINDS LESS RISK OF CANCER IN DAUGHTERS OF DES-EXPOSED MOTHERS

First results of an HEW funded study made public today have confirmed that the synthetic estrogen DES (diethylstilbestrol)--while still a cancer threat to daughters of women who took the drug during pregnancy to prevent miscarriage--may pose less risk than earlier anticipated.

Only four cancers of the genital tract were found among a total of 3,339 DES daughters in the study. No cancers were found among the 1,275 daughters identified through a review of their mothers' medical records and who were most representative of the total population of women exposed to DES before birth. Results of the study sponsored by the National Cancer Institute (NCI) and conducted at four U.S. medical centers were reported to the International Academy of Pathology's U.S.--Canadian Division meeting in San Francisco, and in two papers published in the March issue of *Obstetrics and Gynecology*.

The results are consistent with the conclusions of the HEW DES Task Force. That group last year said that while the risk of cancer is not as great as originally feared, women who took the drug during pregnancy and their children should be examined regularly in order to detect any abnormalities early, in time for effective treatment.

DES was once widely prescribed for the prevention of miscarriages. An estimated 4 million to 6 million persons--women who took the drug while pregnant and their children--are believed to have been exposed to DES, chiefly between 1945 and 1955, but some as late as the 1970's.

The DES study was commissioned in 1974 by the NCI's Division of Cancer Control and Rehabilitation, to determine what risk daughters of women who took DES during pregnancy have of developing adenosis, cancer and other conditions

(more)

associated with the drug. Adenosis is the presence in the vagina of a noncancerous glandular tissue that normally disappears during the development of the genital tract before birth. Some investigators have suggested that adenosis in young women may be a preliminary stage in the development of adenocarcinoma.

Drs. Arthur Herbst, Howard Ulfelder, and David C. Poskanzer of Massachusetts General Hospital reported in 1971 that the mothers of seven of eight female children who had developed clear cell adenocarcinoma of the vagina had taken DES while pregnant.

The DES Adenosis Group (DESAD) comprises investigators at the Baylor College of Medicine, Houston; Massachusetts General Hospital, Boston; the Mayo Clinic, Rochester, Minnesota; and the University of Southern California, Los Angeles.

Data from the DESAD study have been analyzed according to the ways in which the participants were recruited. A large group of DES-daughters was identified by reviewing their mothers' obstetrical records, the second group consisted of women referred to the study by physicians because of their documented exposure, and the third were "walk-ins" with known genital tract abnormalities associated with DES exposure before birth.

A fourth group of women with vaginal changes suggestive of DES exposure before birth was also examined, but obstetrical records were not available to document the history of exposure.

At the San Francisco meeting, Dr. Stanley J. Robboy, a Massachusetts General Hospital pathologist, associate professor of pathology at the Harvard

(more)

Medical School, and a principal investigator in the DESAD study, said that among 1,275 daughters identified through a review of obstetrical records:

* No cancers were found;

* Occurrence of abnormal squamous cell (which are not cancerous) in eigher the vagina or cervix was rare;

* Changes in the lining or the wall of the vagina, including adenosis, were found in 34 percent of the women (much less than had been suspected in some previous investigations);

* Women 26 years of age or older had changes in the vagina less frequently than did younger participants, suggesting that some effects of DES exposure may have less consequence as women grow older.

Only four participants in the entire study had clear cell adenocarcinoma, a rare type of cancer with unusual glandlike appearance when viewed with a microscope, Dr. Robboy reported. These four had been referred to the study by physicians or were in the walk-in group. In two of the patients the cancers were discovered as a direct result of the study examinations. Each patient's cancer was in a very early stage, with a high likelihood of cure.

A benign condition called microglandular hyperplasia (a proliferation of small glands often associated with oral contraceptive usuage) was found in five DES-exposed daughters in the study. This condition, (which is not harmful) can be confused with clear cell adenocarcinoma.

The finding of a 34 percent frequency of changes in the vagina among 1,275 women identified by record review is in contrast to changes in 65 percent of participants referred to the project by physicians, and in 59

(more)

percent of women who had personally requested enrollment in the study because of their known exposure. These results suggest that patients who come to a center, or who are recommended by physicians, are not representative of the total population of daughters exposed to DES. Many other reports have been unduly biased by the methods of recruiting patients to be studied, Dr. Robboy said.

Because identification of DES-exposed patients by obstetrical record review does not select out any isolated group of DES-exposed daughters, "reliable inferences to the general population of DES-exposed daughters should be based on the examination of this segment (women identified through record review) which most clearly represents the overall DES-exposed offspring," said Peter C. O'Brien, Ph.D., Mayo statistician and senior author of one of the papers published in *Obstetrics and Gynecology.*

Among the total number of study participants found to have changes in the vagina and from whom biopsy tissue specimens had been obtained, 45 percent had adenosis. In the past, other investigators had reported identification of adenosis in nearly all women exposed to DES, but the new DESAD data corroborated findings at the Massachusetts General Hospital reported in 1975. Vaginal changes appear to be most common among women whose exposure to DES started during or before the 18th week of their mothers' pregnancies, and involved a large cumulative dose of the drug administered over a long duration.

"Adenosis itself does not appear to be harmful," Dr. Robboy said. He stressed that doctors have been concerned that clear cell adenocarcinoma may arise from adenosis, because almost all vaginal cancers are accompanied

(more)

DES (CONT'D)

by adenosis. Many experts now believe, however, that if adenosis does become adenocarcinoma, the transformation will occur in a miniscule proportion of DES-exposed daughters, possibly as low as one in several thousand.

"At this time no treatment is prescribed for adenosis," said Dr. Raymond H. Kaufman, chairman of the Department of Obstetrics and Gynecology at Baylor College of Medicine and coauthor of both papers. "In our experience in the project, covering several years, no patient with adenosis has developed a cancer. On this basis perhaps the most prudent approach is to be conservative and simply reexamine these young women on a periodic basis."

That older women had vaginal changes less frequently than younger women was described by Dr. O'Brien as an "important and encouraging finding." This fact has become evident because DESAD project particpants now include women as old as 32 years of age, whereas participants in earlier studies generally had not exceeded 25 years. Efforts will be made to identify the factors responsible for the decreasing frequency of changes in older DES-exposed daughters.

"Although these findings concerning DES-exposed daughters are encouraging," said Dr. Arthur C. Upton, Director of the National Cancer Program and the National Cancer Institue, "we must keep in mind that these women are still young. We cannot yet be sure that DES exposure before birth may not adversely affect exposed daughters in later life.

"Therefore, study of the long-term risks of exposure to DES during pregnancy and before birth is continuing. Physicians should be alert to possible effects of DES exposure, and exposed individuals should continue

(more)

DES (CONT'D)

to have regular exmainations, as recommended by HEW's DES task force last year."

In addition to Drs. O'Brien, Robboy and Kaufman, authors of the DES reports include Drs. Ann B. Barnes, Jaime Prat, William R. Welch and Robert E. Scully of the Massachusetts General Hospital; Drs. Kenneth L. Noller and Thomas Gaffey and Ms. Barbara C. Tilley of the Mayo Clinic; Dr. Duane E. Townsend of the University of Sourthern California; Drs. Ralph Richart and Cecilia M. Fenoglio of Columbia University; and Dr. Rodelino Virata of the Gundersen Clinic, LaCrosse, Wisconsin. (Columbia University and the Gundersen Clinic are subcontractees to the University of Southern California and Mayo Clinic. Drs. Prat and Welch are Junior Faculty Fellows of the American Cancer Society.)

###

March 1979

NATURAL GENE CLONES YIELD NEW CLUES TO THE ROLE OF INTERVENING DNA SEQUENCES

This story was especially prepared
for use in NFFN by Mary Lynn Hendrix
of NICHD.

When scientists make a natural gene clone, they pluck one gene out of the 10 million present in the genetic material of the donor organism--in this case a mouse--and use recombinant DNA techniques to splice that gene into the genetic material of a bacterium or bacterial virus. By growing large batches of this simple microorganism, researchers can obtain billions of identical copies of the original gene.

Gene copies produced in this way are called natural gene clones to distinguish them from a second type of clone, made by using messenger RNA as a master pattern. Messenger RNA is a molecule that carries the message of a gene in a somewhat simplified form, so clones made by copying this material have lost some of the features of the original gene. Among the features that are absent in messenger-derived clones but present in natural gene clones are the intervening sequences--a set of peculiar gene inserts whose significance is described in the accompanying article.

Theoretically, any gene from a higher organism can be cloned in its original form, provided that molecular probes are available to find the gene in the first place. New cloning techniques developed at NIH's National Institute of Child Health and Human Development (NICHD) and Stanford University have made it vastly easier to identify a particular gene, so that researchers are now able to clone and study genes that are present in only a couple of copies per cell.

With vast quantities of gene copies available, researchers can examine genes under the electron microscope, determine their exact chemical make-up, and perform many other studies that would have been impossible only a few

(more)

years ago.

Intervening sequences--mysterious bits of apparent gibberish tucked inside the genes of higher organisms--may play an important role in preserving closely related genes and in helping the genetic message to reach its destination within the cell. And "silent" mutations within the intervening sequences may someday provide the key to certain genetic diseases of humans.

These new insights into the make-up of genes come from recent studies carried out with natural gene clones. The clones, each consisting of billions of identical copies of a single gene, permit scientists to make detailed, direct studies of gene structure and function. Several of the techniques used in making these natural gene clones were pioneered by scientists working in the laboratory of Dr. Philip Leder at NIH's National Institute of Child Health and Human Development (NICHD).

Two groups of NICHD-supported researchers are now using natural gene clones to study intervening sequences and other unique features of genes from higher organisms. At the Baylor College of Medicine in Houston, Dr. Bert W. O'Malley and his coworkers have cloned the hen ovalbumin gene, and are using it to find out how hormone-triggered genes work. Dr. Leder and his group have cloned several different globin genes from the mouse, and have determined the exact chemical make-up of one of them--the beta globin major gene. Thus far, beta globin major is the first mammalian gene whose structure is fully known. The researchers have been comparing globin genes in hopes of finding the "on-off" switches that control gene expression.

All of these newly cloned genes are ones that carry blueprints for

(more)

making protein: The ovalbumin gene carries instructions for the synthesis of ovalbumin, the major protein of egg white, while the globin genes code for subunits of the red blood cell protein, hemoglobin.

Every one of these genes contains intervening sequences--long or short stretches of DNA which interrupt the blueprint encoded in the gene, causing it to appear as a series of short bursts of information rather than a single, continuous passage. A mouse globin gene has two intervening sequences; a chicken ovalbumin gene has seven.

How does an interrupted gene manage to send a coherent message to the cell?

The researchers believe that the answer lies in an editing process: the entire gene, which consists of a long molecule of DNA, is used as a master pattern to form another long molecule called presursor RNA. This precursor RNA contains passages derived from the intervening sequences as well as the blueprint sequences of the gene. Somehow, the precursor molecule is chopped apart and spliced back together so that the intervening sequences are lost and the blueprint appears as one continuous message. This edited molecule, called messenger RNA, can be read by the protein-making machinery of the cell.

If the intervening sequences have to be edited out of the gene transcript, why are they present in the first place?

One possible answer comes from new studies conducted by Dr. Leder and Dr. Dean H. Hamer. They have found that intervening-sequence RNA is essential for the production of stable messenger. When a virus is used to tamper with the intervening sequences of a precursor RNA, the blueprint sequences never

(more)

CLONING (CONT'D)

reach the cytoplasm of the cell (where the protein-making machinery is located) in a stable form.

If the intervening sequences are important to gene function, but play no role in determining the final structure of the protein the gene codes for, this fact raises an intriguing possibility: The intervening sequences may carry "silent" mutations--mutations whose existence can only be detected by direct study of cloned genes. It is theoretically possible, Dr. Leder suggests, that silent mutations located outside the blueprint sequences of genes could be responsible for certain blood disorders called thalassemias and for many other genetic diseases of humans. He predicts that researchers will soon be cloning abnormal genes from higher animals and looking for mutations of this sort.

Dr. O'Malley and his coworkers have now found evidence that silent mutations of the intervening sequences do in fact exist. They have cloned ovalbumin genes from differnt chickens and have found that genes with identical blueprint sequences may have differences in their intervening sequences. This discovery, reported by Drs. Eugene Lai, Savio Woo, Achilles Dugaiczyk, Myles Mace, Jr., and Dr. O'Malley in an upcoming issue of the journal *Cell*, indicates that genetic differences between individuals may be far greater than previously believed.

In the December issue of *Cell*, Drs. David Kinkel, Shirley Tilghman and Dr. Leder report the complete sequence analysis of the beta globin major gene of the mouse. They have found certain passages inside and outside the gene that may serve as "start" and "stop" signals from RNA polymerase--the enzyme

(more)

makes the precursor RNA. Their work also confirms previous suspicions that the intervening sequences cannot serve as a source of instructions for making protein. These sequences turn out to be shot through with nonsense passages which would frustrate the protein-making machinery of the cell.

In addition to acting as a reservoir of silent mutations, the intervening sequences may play an important evolutionary role, preventing errors in the inheritance of closely related genes. This suggestion comes from studies carried out by Dr. Leder and his coworkers--Drs. David Tiemeier, Shirley Tilghman, Fred Polsky, Jon Seidman, Marshall Edgell, David Konkel, Henry Miller, Dean Hamer, and Jon Seidman, along with Aya Leder, Barbara Norman, and Margery Sullivan. These researchers have taken advantage of the fact that the mouse has several globin genes, which code for nearly identical subunits of the hemoglobin molecule. All the globin genes are believed to be derived from a single ancestral gene that accidentally duplicated and reduplicated itself hundreds of millions of years ago.

The various members of the globin gene "family" all turn out to have intervening sequences in exactly the same places. But these sequences differ radically in their content, so much so that intervening sequences from different globin genes are barely able to "recognize" each other when brought together in the test tube. The only points of similarity between intervening sequences are at their edges, where they join up with the blueprint sequences of the gene.

This failure in recognition suggests that intervening sequences may help to prevent "sibling" genes from mistakenly pairing with each other, instead of their proper mates, at the time of sexual division of the cell.

(more)

CLONING (CONT'D)

This protective feature would lessen the danger of unequal crossing-over, an error of inheritance that occurs when chromosomes pair incorrectly. If the intervening sequences help to preserve multiple copies of valuable genes, that would explain why the sequences have remained in the genetic library of higher organisms for so many millions of years.

Researchers in both laboratories are now examining cloned genes for clues to the signals that guide the processing of the gene transcript. At either end of the intervening sequences of globin genes, Dr. Leder and his coworkers have found short stretches of DNA that don't vary from gene to gene. These passages, the researchers believe, may signal the processing enzymes to "cut and splice here." Dr. O'Malley and his group, working in association with Dr. George Brownlee of the MRC Laboratory of Molecular Biology in England, have also found evidence of marker passages located at the junctures between intervening sequences and blueprint sequences. Their findings are reported in the October 12 issue of the journal *Nature*. Presumably, mutations in these marker passages could also interfere with the processing of genetic message.

Both groups of researchers are also exploring sequences of DNA located on the outside of the gene proper, and cloned along with it. These so-called "flanking sequences" may contain the on-off switches of the gene. Leder and his coworkers hope to discover how the various globin genes are switched on simultaneously in the course of development.

O'Malley and his group want to find out how a hormone molecule and its receptor attach to the ovalbumin gene and turn it on. They plan to combine

(more)

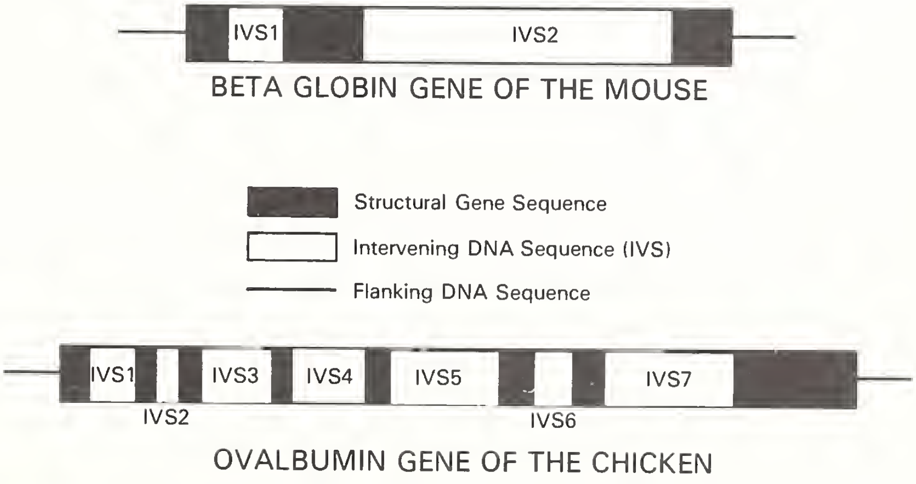
CLONING (CONT'D)

the steroid sex hormone progesterone with purified progesterone receptor, and to examine the interaction between these two molecules and the ovalbumin gene. They have just cloned another hormone-activated gene--the ovomucoid gene--and are planning to analyze its function as well.

Researchers in both groups believe that the discoveries reported thus far represent only a fraction of the knowledge that will eventually be gained from the natural gene clones.

"Now that we know what the ovalbumin gene looks like," says Dr. O'Malley, "we're going to be better able to understand its function--its normal function, its behavior under the influence of hormone, and its function in genetic disease."

"Within the next few years," Dr. Leder predicts, "natural gene clones will be established at dozens of laboratories all over the world." Molecular biologists will then be able to take a first-hand look at genes that are presently known only by their ultimate products. The result will undoubtedly be the discovery of new kinds of regulatory mechanisms as well as new classes of mutations.

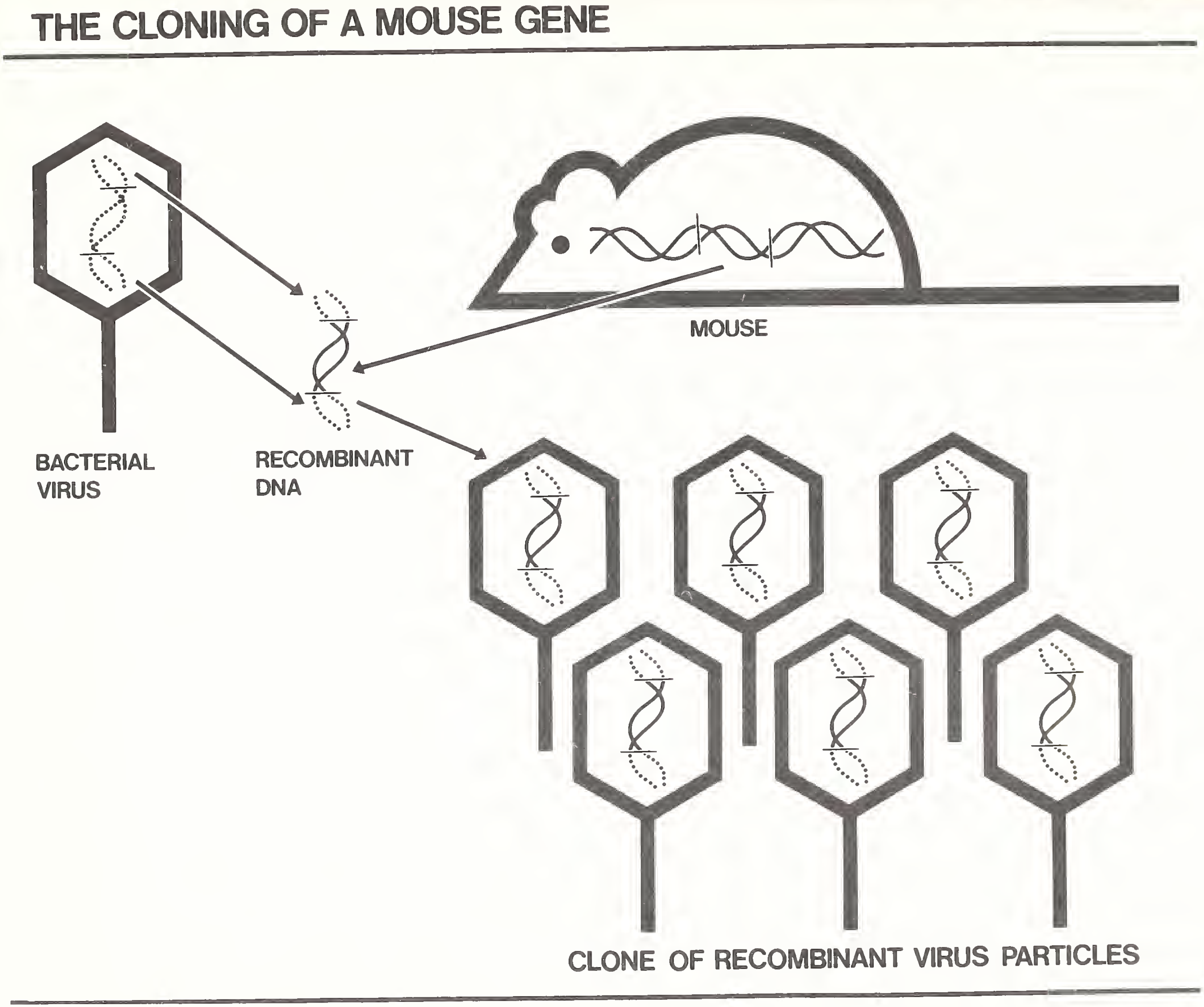


BETA GLOBIN GENE OF THE MOUSE

OVALBUMIN GENE OF THE CHICKEN

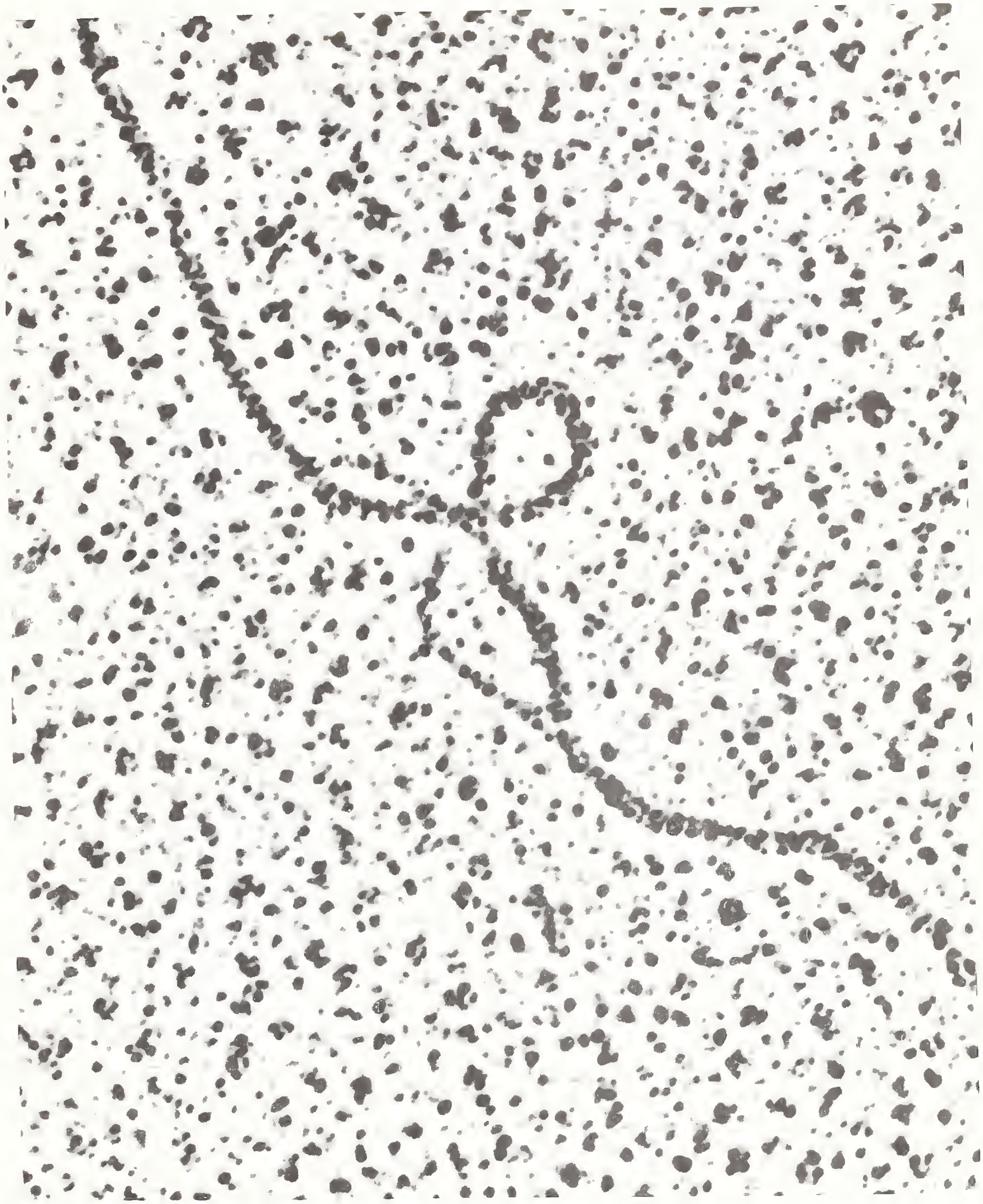
(more)

These are diagrams of the beta globin major and ovalbumin genes, showing the intervening sequences (IVS). (NIH Photo # 1618)


THE CLONING OF A MOUSE GENE
BACTERIAL VIRUS
RECOMBINANT DNA
MOUSE
CLONE OF RECOMBINANT VIRUS PARTICLES

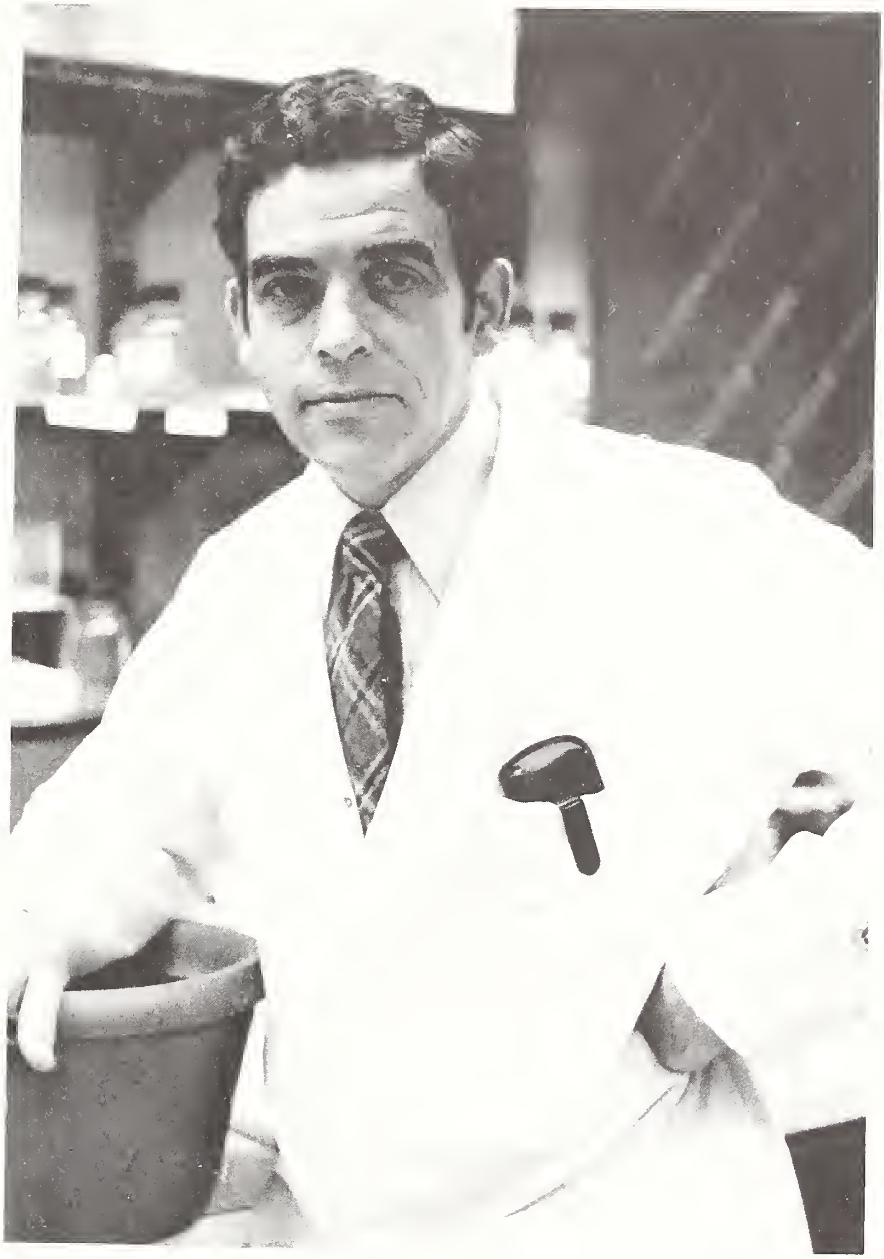
Making a natural gene clone: A gene from a mouse is inserted into the DNA of a bacterial virus. The modified virus is then grown in large batches, each containing billions of identical copies of the animal gene. (NIH Photo # 1619)

(more



Beta globin major gene of the mouse, tagged with matching RNA, is photographed under the electron microscope. (NIH Photo # 1620)

(more)



Dr. Philip Leder, a pioneer of natural gene cloning, in his laboratory at the National Institute of Child Health and Human Development (NICHD). (NIH Photo # 1621)

###

DIABETES GENES PROTECT "THRIFTY" MICE FROM STARVATION

The genes which code for diabetes and obesity in mice present the classic good news/bad news dilemma. The good news is that mouse heterozygotes, which inherit only a partial dose of obesity or diabetes genes traits, show increased metabolic efficiency and a remarkable ability to withstand starvation. The homozygotes, which inherit the full obesity or diabetes trait, are also more metabolically efficient and starvation resistant, but suffer the "bad news" of the decreased lifespan and general debilitation.

Partial inheritance of these two normally bad news genes has been called the "thrifty" trait or genotype. In human populations, those individuals with this thrifty trait could utilize a limited food supply more efficiently and would have a distinct survival advantage in times of famine. This may explain the persistence of the diabetes genotype in animals and man despite strong negative selective pressures.

Dr. Douglas Coleman of the Jackson Laboratory in Bar Harbor, Maine reports the results of his study of the thrifty genotype in two strains of mice in the February 19, 1979 issue of *Science*. Dr. Coleman's research is supported in part by the National Institute of Arthritis, Metabolism, and Digestive Diseases.

It is not possible to identify diabetic heterozygotes in humans but several strains of mice exhibit marker mutations. The BL/6 and the BL/K strains used in this study show a consistent repulsion of a coat-color "misty" recessive gene on the opposite chromosome from the diabetes mutation. Thus all normal BL/6 and BL/K mice are gray, whereas heterozygote mice of those strains with the diabetes trait are black. Except for coat color, the heterozygotes are normal in all other measurable parameters including body weight and blood sugar.

(more)

DIABETES GENES (CONT'D)

In the experiment, normal mice from the two strains, heterozygote mice with the diabetes trait and heterozygote BL/6 mice with the obesity trait were housed individually and given free access to identical food and water for a week. Baseline measurements on all mice were done in this time. They were then subjected to a total fast with water freely available.

A difference between the two strains in starting body weight at the initiation of the fast was obvious. The BL/6's routinely weigh 35 grams or more, the BL/K's rarely attain 35 grams. The heavier BL/6s survive fasting better than the lighter BL/K's.

The BL/6 heterozygote with the diabetes trait survived total fast for 12.2 days, 2 days longer than the normals, the BL/6 heterzygotes with the obese trait survived 1.4 days longer than the normals. The similarity in the prolonged lifespan suggests that the obese and diabetic mutations confer about the same amount of thriftiness in the BL/6 strain.

The BL/K heterzygote mice with the diabetic trait survived total fast 10.5 days, 3.3 days longer than the BL/K normals, even though their starting body weight was less than 30 grams. This extra increment in lifespan might represent a synergistic interaction of the mutant gene with the BL/K genetic background.

Insulin levels in the heterozygote mice used in this experiment were completely comparable to those of the normals. Although no increase was apparent, it may be that the heterozygote mutation confers extra sensitivity to normal plasma insulin concentrations in promoting increased metabolic efficiency. Other possible starvation survival mechanisms present in the heterozygotes

(more)

DIABETES GENES (CONT'D)

may be in the nature of fat storage, or in temperature regulation defects which are found in diabetic and obese mice.

Subsequent unpublished research done by Dr. Coleman has found that completely homozygous diabetic or obese mice can withstand total fast up to 40 days, which hints at the "good news" selective advantage found in partial inheritance of those "bad news" genes.

Certain human populations found in desert of less affluent regions have shown a higher relative incidence of diabetes than found in groups inhabiting regions with a more regular and ample supply of food. The results of this research points to a possible explanation as to why the good news/bad news mutation of diabetes has survival value in its thrifty genotype.

###

NEWS & FEATURES From NIH

March 1979

US-USSR BEGIN COLLABORATIVE RESEARCH IN EYE DISEASES

The United States and the Union of Soviet Socialist Republics have begun formal collaboration in research on eye diseases, which will be announced March 7, by Joseph A. Califano, Jr., Secretary of Health, Education, and Welfare.

The two nations will engage in cooperative vision research projects and scientific exchange under provision of the U.S.-U.S.S.R. Program for Health Cooperation. Vision research is thus afforded the same priority in the program as the other ongoing U.S.-U.S.S.R. collaborative health research efforts in cancer, cardiovascular diseases, artificial heart, environmental health, schizophrenia, arthritis, and influenza and acute respiratory diseases.

In making this announcement, Secretary Califano said, "Collaborative research between nations not only provides an international forum for the exchange of ideas and scientific information, but helps spread the fruits of health research to all peoples of the world. This new collaboration between the U.S. and U.S.S.R. in vision research comes at a time when experts are estimating that the number of blind people worldwide, now estimated at 40 million, could double by the end of this century. By working with the Soviet Union to foster eye research, we hope to contribute to the prevention of such an enormous increase in global blindness and at the same time work to improve the well-being of those who already suffer from disabling eye diseases."

Coordinating the cooperative vision research program for the U.S. is Carl Kupfer, M.D., Director of HEW's National Eye Institute. Professor Michail M. Krasnov, M.D., Director of the All-Union Scientific Research Institute of Eye Diseases of the Soviet Ministry of Health, is coordinator for the U.S.S.R.

The decision to embark on a formal collaboration for research in eye

(more)

EYE DISEASE (CONT'D)

disease was reached after a successful exchange of visits and subsequent informal contacts between Drs. Kupfer and Krasnov over the past five years. This exchange has resulted in the identification of specific research projects and of individual scientists who would participate initially in a vision research exchange program.

Detailed plans for implementing the new collaborative effort were developed at the Seventh Session of the U.S.-U.S.S.R. Joint Committee for Health Cooperation held in Moscow. These call for initial projects in laser treatment of glaucoma, in research on retinal degenerations, and in studies of cataract.

Commenting on the new cooperative effort, Drs. Kupfer and Krasnov issued the following joint statement. "We look forward to a highly productive collaboration in vision research. A number of important opportunities exist in this field in which scientists from our two nations can offer their unique expertise and capabilities, not only for our mutual benefit but for the benefit of people everywhere who suffer from blinding and disabling eye diseases."

###

NEWS & FEATURES From NIH

March 1979

DECLINE IN FAT METABOLISM MAY BE CAUSE OF SHORTENED LIFE

Many of the diseases which shorten lifespan and cause excessive illness in the later years may be the partial result of our decreasing ability to utilize or metabolize fat with age. Studies supported by NIH's National Institute on Aging (NIA), on rats indicate that dietary restrictions imposed early in life may markedly delay this decline thereby delaying the onset of age-related diseases such as diabetes and coronary heart disease.

NIA grantee, Dr. Edward J. Masoro of the University of Texas Health Science Center in San Antonio, decided to examine the relationship between calorie-restriction and age-related decline in fat metabolism efficiency after earlier work showed that food-restricted animals far outlived animals permitted to eat freely. Masoro and his colleagues examined three variables: age-related decline in responsiveness to the hormone, glucagon; age-related decline in responsiveness to adrenalin; and age-related accumulation of serum lipids in the blood.

Both glucagon and adrenalin promote fat metabolism by releasing fat from adipocytes (fat cells) and carrying it to the blood where the body converts it into energy. Normally, as the animal ages, its adipocytes become less responsive to these hormones, a factor which may lead to obesity. However, in rats whose caloric intake is restricted from early life, these declines in hormone responsiveness are substantially delayed. In addition, the increasing accumulation of serum lipids, which occurs with advancing age and is implicated for man in coronary heart disease, is also delayed in early food-restricted animals.

Equally significant is this group's observation of certain adipocyte

(more)

changes in selected tissues of the rat which contradict current theory on the biology of fat cells. For years, scientists have believed that the life-long number of fat cells is determined in the first few weeks of life by pre-weaning nutrition. These studies on the rat show that dietary restriction beyond the weaning period can cause changes not only in the size of adipocytes but also in the number of adipocytes in the fat depot surrounding the kidneys. Calorically-restricted animals maintain fewer and smaller fat cells in these tissues than free-fed animals. Also contrary to the current belief that adipocyte number remains constant throughout adulthood is the discovery that, regardless of food intake, all rats acquire additional fat cells in the kidney depot with advancing age.

Finally, these grantees observed that food-restricted rats maintain a sleek, smooth, bright physical appearance and active, alert behavior patterns typical of chronologically younger animals. This early restriction in calories also enhances the animal's ability to maintain optimal muscle function.

These studies are both encouraging and discouraging. While they suggest the possibility that certain age-related diseases may be delayed through early caloric restriction, they also reveal a possible explanation for the tendency towards obesity--more cells for deposit of fat and more difficulty in utilizing this fat, once deposited.

This work was presented by Dr. Masoro at the annual meeting of the American Association for the Advancement of Science, January 3-8 in Houston, Texas.

###

EWS & FEATURES From NIH

March 1979

ANTIBIOTIC RESISTANCE CAN TRANSFER IN MOUTH

Microbiologists at NIH's National Institute of Dental Research (NIDR) report that resistance to antibiotics is transferred among a number of species of streptococcal bacteria that live in the mouth. Some of these microorganisms can cause human diseases such as strep-throat, endocarditis (rheumatic heart disease) and septicemia (blood poisoning).

(The steady increase of bacterial drug resistance in recent years has disturbed many physicians and biologists and now concerns dentists and veterinarians). The new findings underscore a recommendation for cautious prescribing of antibiotics in order to assure that these medicines will remain effective against serious infections.

Heretofore bacterial drug resistance was known to increase among patients who took antibiotics frequently or for long intervals. Microbiologists also knew that much antibiotic resistance is transferred by a process called conjugation which requires close contact between bacteria. In conjugation the genetic traits that confer this resistance are passed directly from one bacterium to another. The genes and others that control the conjugation process itself have been located on plasmids which are circular pieces of DNA. Plasmids are separate from and reproduce independently of chromosomal DNA. Hence all bacteria do not conjugate and those that do are not always resistant to antibiotics.

Previously bacteriologists thought that antibiotic resistance was transferred only among one division of bacteria--the Gram-negative species--and was largely limited by conjugation between closely-related species, for instance, strains of the common intestinal organism *Escherichia coli*.

(more)

RESISTANCE (CONT'D)

Now the NIDR scientists find that resistance to several antibiotics also occurs among the other great division of bacteria -- the Gram-positive forms, and that it may be transferred by conjugation between members of different species, many of which are found in samples of bacterial plaque from mouths and teeth of dental patients. The scientists also note that many disease-causing organisms are in this Gram-positive group.

The bacteriologists began their studies by purifying a plasmid that carries genetic resistance against two antibiotics, erythromycin and lincomycin. The purified DNA of these plasmids from an intestinal organism called *Streptococcus faecalis* was added to a culture of a different, non-resistant streptococcus *(S. anginosus)* derived from human throat, skin, and other tissues. Next, the investigators identified newly-resistant *S. anginosus* cells by adding the antibiotics to the medium and recovering the survivors.

Subsequently, the investigators found that when resistant *S. anginosus* cells were mixed with any of a number of streptococci isolated from patients' mouths, resistance to both antibiotics could be transferred to the new species.

The scientists are now studying resistance of oral bacteria to other antibiotics. In one investigation of patients treated with tetracycline for severe periodontal gum disease, they note that all samples of human dental plaque taken before treatment contained some microbes resistant to tetracycline, but that the proportion of resistant bacteria increased dramatically after only two weeks of tetracycline therapy. The scientists have found that in some of these bacteria, tetracycline resistance is associated with plasmid DNA.

The research, presented by Drs. Donald J. LeBlanc and Edward J. St. Martin

(more)

RESISTANCE (CONT'D)

together with Robert J. Hawley and Linda N. Lee at the Seventh International Congress on Streptococci and Streptococcal Diseases, Oxford, England, September 11-15, 1978, will appear in the proceedings of the meeting.

###

NEWS & FEATURES From NIH March 1979

ORAL CONTRACEPTIVES MAY NOT CAUSE BIRTH DEFECTS

Despite evidence that oral contraceptives may pose some risks to the women who use them, the Pill apparently does not present any major hazards to the offspring of these women.

Previous research by Harvard School of Public Health epidemiologists had found that oral contraceptives have no adverse effects on the birth weight, miscarriage or still birth rate, nor any effect on the gender of infants born to women who had used the Pill.

Now, in a new study based on that research, the Harvard investigators report that oral contraceptives apparently have also been absolved as a major cause of birth defects.

The Harvard scientists, who are supported in part by a grant from NIH's National Institute of Child Health and Human Development (NICHD), report that when a woman conceives at least one month after discontinuing use of oral contraceptives, her chance of bearing a child with a birth defect is no greater than that of a woman who has never used the Pill or has not used it within three years of conceiving.

Even for those infants conceived within a month of their mothers oral contraceptive use, the Harvard scientists found a malformation rate only slightly greater than in the group whose mothers were either non-users or had not used the Pill within 36 months of conception. This slightly greater rate, the Harvard team says, could be explained by chance.

Previous research has linked two types of birth defects -- heart malformation and congenital limb reduction -- with use of oral contraceptives. But the small increase in risk associated with oral contraceptive use appears to

(more)

NTRACEPTIVES (CONT'D)

be limited to infants whose mothers used oral contraceptives after conception, according to the Harvard researchers. They add, "It appears likely that the increase in risk from oral contraceptives is less than that from prescribed hormonal drugs or from hormonal pregnancy tests."

In this study, the birth certificates and hospital records of 7,723 infants whose mothers had used oral contraceptives were examined. The malformation rate was 3.3 percent for infants conceived more than three years after their mothers had discontinued oral contraceptive use compared to a 3.8 rate for the 5,535 infants conceived within 36 months of their mother's taking the Pill.

This latter rate was pushed up by the finding of a 4.3 malformation rate among the 1,448 infants conceived within one month of their mothers' using oral contraceptives; this group may include some infants whose mothers took the Pill after conception, unaware that they were pregnant. A rate of 3.6 percent was found for infants conceived more than one month and less than three years after their mothers used oral contraceptives.

There was no association between length of prior oral contraceptive use and the incidence of birth defects. Likewise, there was no difference in the severity of the birth defects noted in the infants born to women who had used the Pill within 36 months of conception compared to mothers who had never used the Pill or had used it more than three years prior to conception.

The birth defects study was reported by Dr. Kenneth J. Rothman and Ms. Carol Louik in Vol. 299, No. 10 of the *New England Journal of Medicine*.

###

NEWS & FEATURES From NIH

March 1979

INITIAL DNA RISK ASSESSMENT STUDIES FIND INFECTION HAZARD MINIMAL

For a number of years, NIH scientists and others have pursued an exciting area of basic research now called recombinant technology. Simply stated, this technology involves transferring a piece of genetic material from one species into another. Using this technology, scientists have employed common bacteria to produce medically important substances as insulin and growth hormone.

Much of the early controversy relating to recombinant DNA research was concerned with hypothetical risks. This has subsided. The safety requirements for conducting recombinant DNA research were relaxed last December when DHEW Secretary Califano approved a revision of the NIH guidelines for conducting this type of research.

The initial risk assessment studies related to this research were undertaken by two NIAID scientists, Drs. Malcolm Martin and Wallace Rowe, at the maximum safety facility of the Frederick (Maryland) Cancer Research Center. They used the mouse polyoma virus as a model in these initial studies.

Results of these initial risk-assessment studies are being published in two articles in the March 2 issue of *Science*. The studies have led Dr. Martin to conclude that the mouse virus in the recombinant molecule was far less infectious than the original mouse virus. The results also suggested that infection caused by bacteria containing recombinant viral DNA is highly unlikely.

Risk assessment is a highly complex area of research, progressing in increments, and these experiments represent only one part of a larger program called for by Secretary Califano when he annouced the relaxation of the NIH guidelines last December.

Scientists from the National Institute of Allergy and Infectious Diseases

(more)

(NIAID) report that virus infection caused by bacteria containing recombinant DNA molecules is highly unlikely. This conclusion is based on results from the initial polyoma virus risk assessment experiments to evaluate the potential risks associated with recombinant DNA research.

NIAID virologists -- Drs. Malcolm Martin and Wallace Rowe and co-workers -- carried out the experiments under P4 physical containment conditions at Fort Detrick, Frederick, Maryland and at NIH in Bethesda. The studies were designed to examine the ability of bacteria carrying a recombinant molecule containing polyoma DNA to cause polyoma virus infection in mice.

The polyoma system was selected because the virus and its DNA have been well characterized and mice of all ages are highly susceptible to polyoma infection. Once infected, mice develop a serum antibody response readily detectable by a simple laboratory test. The polyoma virus has not been found to replicate in human cells.

In two separate types of experiments, the scientists used restriction enzymes to construct a series of recombinant molecules containing polyoma DNA linked with DNA from either a bacterial plasmid or bacteriophage (virus that infects bacteria). Recombinant molecules of each vector type -- plasmid or phage -- were inserted into the bacterial host (*E. coli)* for cloning. The experiments were carried out using an enfeebled derivative of *E. coli* not expected to survive in the intestinal tract.

After propagation of the recombinant molecules in the bacterial host was determined, mice were then fed or injected with the infected bacteria and tested for evidence of polyoma infection using the antibody production test.

(more)

NA RISK (CONT'D)

ecombinant DNA alone was also tested for infectivity both in mice and in cul-ured mouse cells.

In no case was polyoma infection observed in mice or mouse cells exposed o massive doses of bacteria carrying the recombinant molecules. Furthermore, n these cases where only a single copy of the polyoma DNA was contained in the ecombinant molecule, injection of the recombinant molecules as free DNA never nduced an infection. Since these recombinants contained the entire potentially infectious polyoma DNA, these experiments showed that being contained in a recombinant molecule renders the viral DNA unable to replicate and cause infection in mouse cells.

One of the phage recombinants contained two copies of the polyoma DNA, unlike the plasmid recombinants which contained only single copies. In theory, recombinants with two copies of the polyoma recombinants with two copies of the polyoma DNA are more likely to cause infection since the polyoma genome can be reconstructed by intramolecular recombination. Polyoma infection was observed in some of the mice injected with large doses of DNA from these double-copy recombinants. However the scientists found no evidence of infection in mice fed or inoculated with whole, live bacteria carrying the double-copy polyoma recombinants. The investigators suggest that the absence of infectivity may be due to an inhibition of phage replication in the bacteria once it is injected into mouse tissue. Feeding the mice with bacteria was not expected to cause infection, since the viral DNA had been shown to be non-infectious by this route.

In addition, from these results and others, the scientists conclude that it is highly unlikely for recombinant molecules containing more than one copy of viral DNA to be produced during the course of a recombinant DNA experiment,

(more)

DNA RISK (CONT'D)

particularly during a shotgun experiment. If double copies are produced, they frequently revert to a single copy in the bacteria used for their propagation.

Based on their results, the scientists state that, in mice, polyoma DNA contained in recombinant DNA molecules is far less infectious (between 10 million and a billion times less) than the original polyoma virus. In addition, when administered by mouth or in live bacteria, recombinant polyoma molecules were never observed to cause infection. Furthermore, no free viral DNA or virus growth was observed in the bacteria carrying the recombinant DNA molecules.

These conclusions basically confirm much of what was anticipated by infectious disease experts concerning the infectivity of bacteria carrying recombinant viral DNA. The investigators predict that a similar reduction in, or lack of, infectivity will be observed in other experiments involving recombinant DNA molecules obtained from other animal DNA viruses.

However, the investigators stress that no single experimental system can declare recombinant DNA research "dangerous" or "safe." Risk assessment of a complex area of research progresses in increments. Since it is conceivable that the bacteria carrying the polyoma recombinants could induce tumor formation in laboratory rodents, experiments to determine this possibility are currently underway.

According to the scientists, an important objective of the polyoma experiments was to find the extent to which recombinant DNA molecules can move from bacteria to mammalian cells in functional form. The rarity of infection caused by the double copy recombinant molecules suggests that movement of the recombinant molecules is not an efficient process. If this is the case, reduced

(more)

tumorigenicity, like infectivity, might also be expected in further experiments involving recombinant polyoma DNA.

Mark A. Israel, Hardy W. Chan, Claude F. Garon, Wallace P. Rowe and Malcolm A. Martin of the DNA Recombinant Research Unit and the Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland reported their research in two papers, Molecular Cloning of Polyoma Virus DNA in *E. Coli* I. Plasmid Vector System, and Molecular Cloning of Polyoma Virus DNA in *E. Coli* II. Lambda Phage Vector System, in the March 2, 1979, issue of *Science* magazine.

###

NEWS & FEATURES From NIH

March 1979

In Perspective:

RABIES TRANSMITTED THROUGH CORNEAL TRANSPLANT

The first case of rabies transmitted between humans through corneal transplant is described by scientists from the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) in the March 15, 1979, issue of *The New England Journal of Medicine.*

Dr. Sidney A. Houff and colleagues report that a 37-year-old women died of rabies 50 days after receiving a corneal transplant from the forester whose death was thought to be due to Guillain-Barre syndrome.

The woman's death was also first attributed to Guillain-Barré syndrome, but tests conducted at the NINCDS Infectious Disease Branch revealed rabies virus in her eyes and brain. Rabies virus was later found in the eyes of the forester.

Rabies vaccine was given as a preventive measure to at least 60 members of the medical staff who cared for the victims.

A diagnosis of rabies can be easily missed, the authors point out, because in up to 20 percent of cases, symptoms mimic Guillain-Barré syndrome--a neurological disorder characterized by progressive paralysis. Rabies was not initially considered, since neither the forester nor the woman had a history of an animal bite.

The authors advise caution when approving certain patients as organ donors. Patients with postinfectious polyneuritis (inflammation or degeneration of peripheral nerves) should probably not be accepted, they suggest, nor should patients with a neurologic disease suspected of being caused by a virus.

###

Editors of publications may request a glossy print of the numbered photographs that appear in this issue.

Mrs. Joyce F. McCarthy
National Institutes of Health
Building 31, Rm. 2B-10
Bethesda, Maryland 20205

Dear Mrs. McCarthy:

Please send me one glossy print of the numbered photographs checked below:

1618 _____

1619 _____

1620 _____

1621 _____

Name: ____________________

Title: ____________________

Publication: ____________________

Address: ____________________

City, State, Zip: ____________________

Telephone: ____________________

NEWS&FEATURES FROM NIH

PORTFOLIO — DIABETES RESEARCH

JULY 1979

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE■Public Health Service■National Institutes of Health■Office of Information■Bethesda, Maryland 20205

LIBRARY
AUG 10 1979
NATIONAL INSTITUTES OF HEALTH

Diabetes

Thomas H. Flavin, Acting Editor
NIH News Branch
Building 31, Room 2B-10
Bethesda, MD 20205
Phone: (301) 496-1206

Designed by Joyce F. McCarthy

PORTFOLIO ON DIABETES RESEARCH

by

Lester B. Salans, M.D., Associate Director for Diabetes, Endocrine, and Metabolic Diseases, NIAMDD

Diabetes mellitus is one of the most serious medical and public health problems facing this country today. It affects millions of Americans, and its prevalence in the population appears to be increasing. The enormous burden that diabetes inflicts upon individuals and society as a whole is readily apparent when the debilitating and chronic physical, emotional and financial consequences of this disease are considered. Indeed, virtually every system of the body is affected, resulting in increased morbidity and mortality due to a wide variety of pathologic and functional disorders.

In the diabetic individual, there is an impairment of insulin activity. Either the body doesn't produce enough insulin, or the available insulin is somehow prevented from influencing its target tissues and cells, and the insulin is unable to perform its primary function. Because of this impairment, glucose is not properly utilized by the body, and excessive glucose accumulates in the blood and tissues and overflows into the urine. Too much glucose in the blood and urine are signs of diabetes that lead directly to the classic diabetic symptoms of excessive urination, thirst and hunger. The inability of insulin to perform its normal function also results in the body's impaired ability to utilize fats and proteins normally; abnormalities of fat and protein metabolism are characteristic of diabetes.

Diabetes is also characterized by long-term complications which involve the blood vessels, the heart, the nervous system, kidneys, and eyes. Diabetes is a leading cause of heart and kidney disease and is the principal cause of new blindness in adults in the United States. As a consequence, the life expectancy of the diabetic population is decreased. How these chronic complications are related to the abnormalities of glucose, protein and fat metabolism, and insulin remains to be determined with certainty.

Diabetes and its complications are leading causes of outpatient physician visits and hospitalization. The direct and indirect impact of diabetes on the nation's economy has been estimated at more than $5 billion per year -- even without considering the costs of the serious and devastating complications.

The eventual solution to this major health problem lies in research - the search for the fundamental causes of diabetes, and through an understanding of the causes, the development of a cure or -- better -- a method of preventing the disease. Basic and clinical research into the cause, cure, prevention, and better treatment of diabetes is substantially supported by various Institutes of the National Institutes of Health (NIH). The National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) has the lead responsibility for the Federal government's program of research in the field of diabetes. In addition, there has been increased support of diabetes research by several groups in the private sector, including the American Diabetes Association, the Juvenile Diabetes Foundation and the Kroc Foundation.

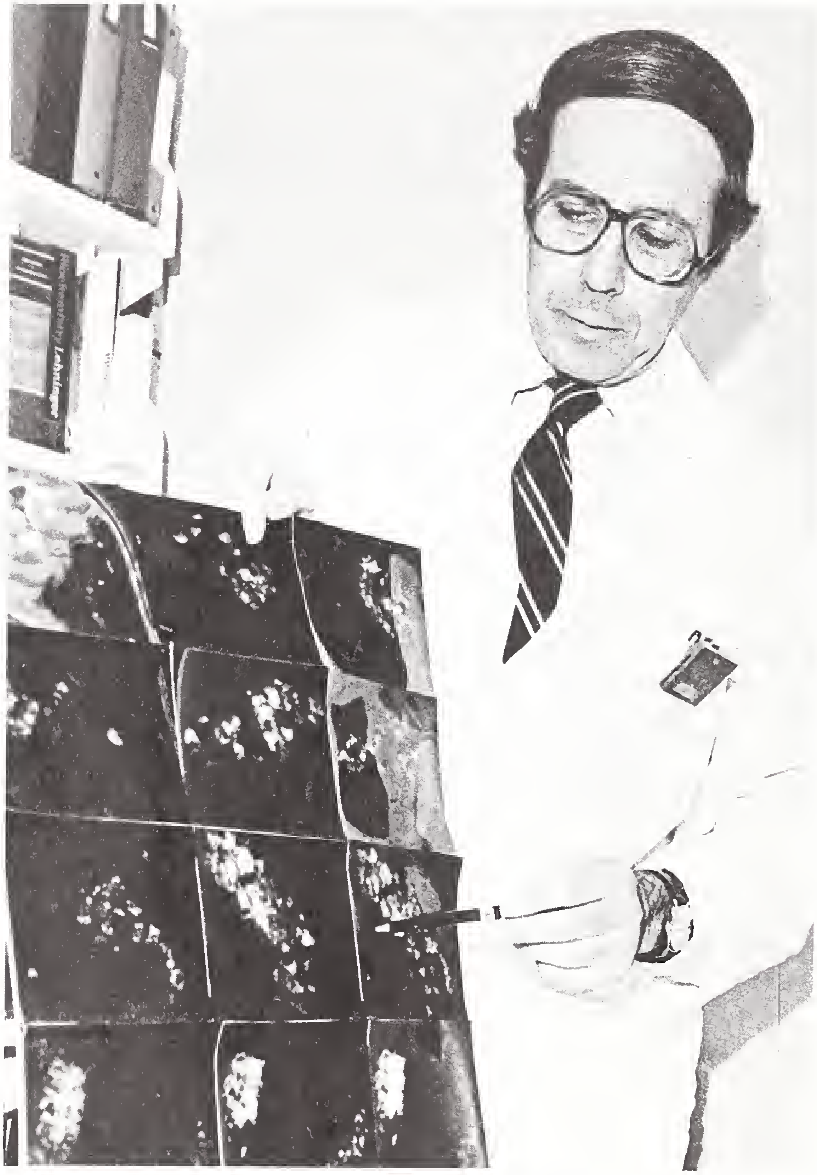
Current diabetes research is a very extensive, broad-spectrum effort spanning the range of many disciplines in biomedical, epidemiologic and behavioral science. Particular emphasis is being directed toward the: 1) etiology, pathogenesis and epidemiology of diabetes with particular emphasis on genetic, viral and immunologic components of diabetes; 2) synthesis, secretion, and action of hormones, with special emphasis on insulin, glucagon, somatostatin and the gastro-intestinal hormones; 3) use of recombinant DNA techniques to produce insulin; 4) complications of diabetes-particularly those of the heart, the eyes, the kidney, the nervous system and pregnancy; 5) improved diagnosis and monitoring of the diabetic state through such potential tools as genetic markers, capillary basement membrane thickening, altered platelet function, fibrinolysis, and glycosylated hemoglobin levels; and 6) refinement and development of new treatment methods for diabetes and its complications. These new methods include pharmacology, pancreatic transplantation, the development of an artificial device to sense the concentration of glucose in the blood and deliver insulin to the blood, and photocoagulation of damaged retinal blood vessels.

Considerable and exciting progress is being made through the research efforts of investigators throughout the world. This portfolio describes work being performed in one area by some of the scientists who are conducting NIH-supported research in diabetes and related endocrine and metabolic disorders.

For more information contact Betsy Singer at (301) 496-3583,
Patricia G. Sheridan at (301) 496-3583, or
Lois F. Lipsett at (301) 496-7433.

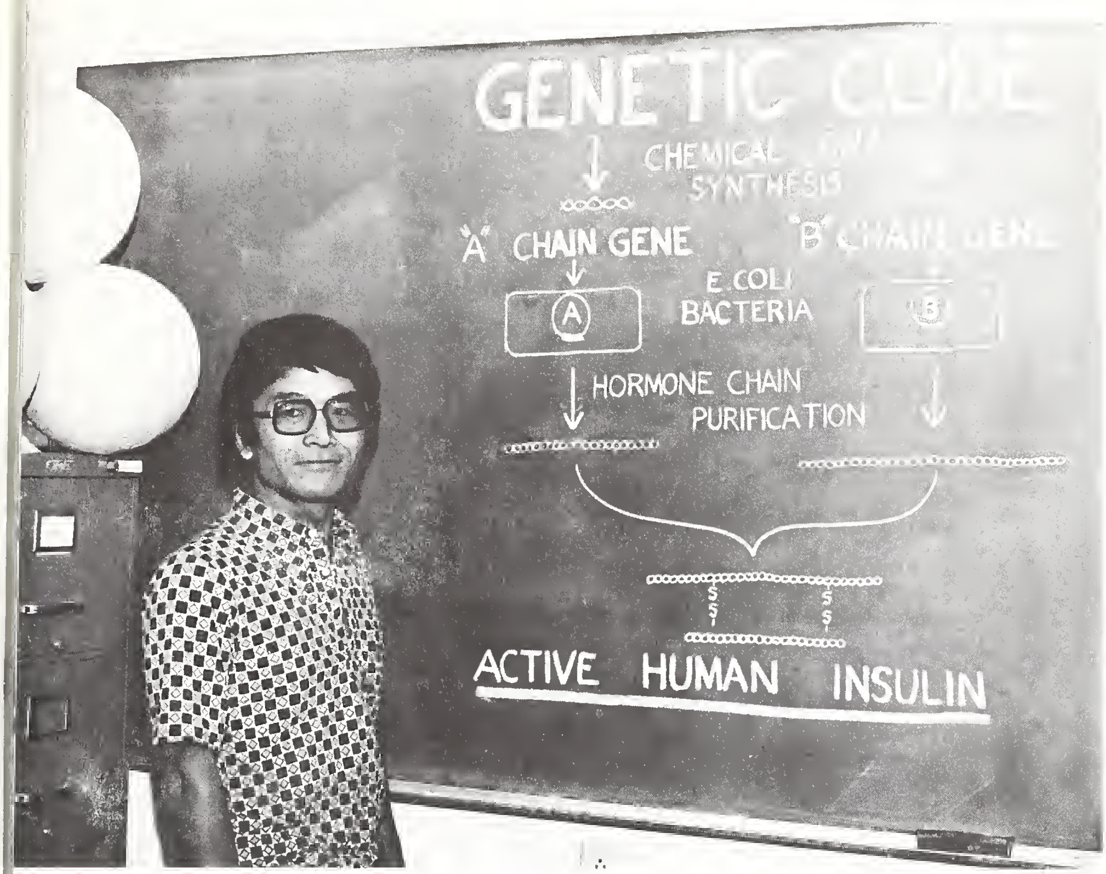
Diabetes

Bethesda



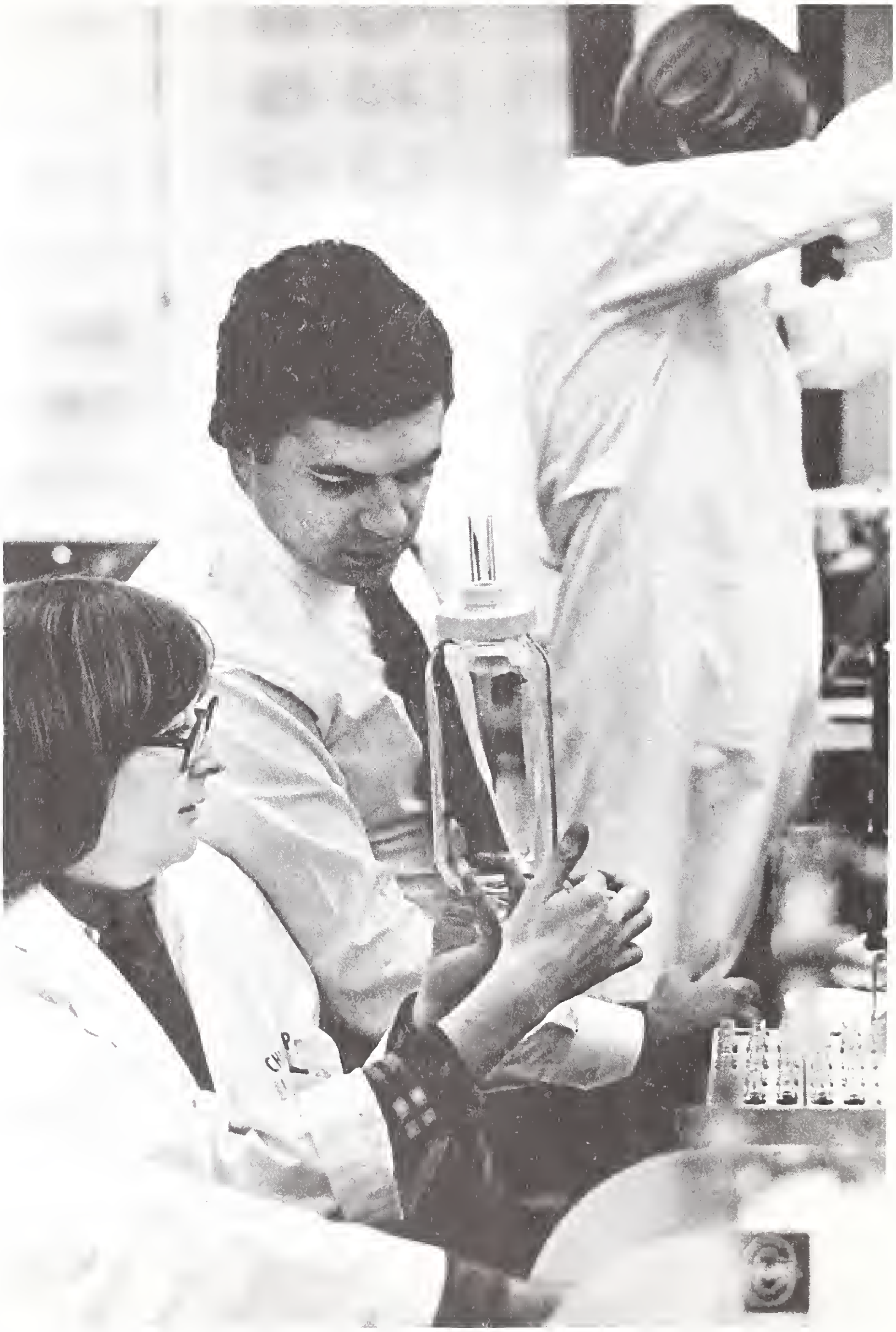
Abner Notkins, M.D., is Chief, Laboratory of Oral Medicine at the National Institute of Dental Research, the National Institutes of Health, Bethesda, Md. In his laboratory, Dr. Notkins is studying virus-induced diabetes and viral immunology and immunopathology. (NIH Photo #DP-1) abetes

arte



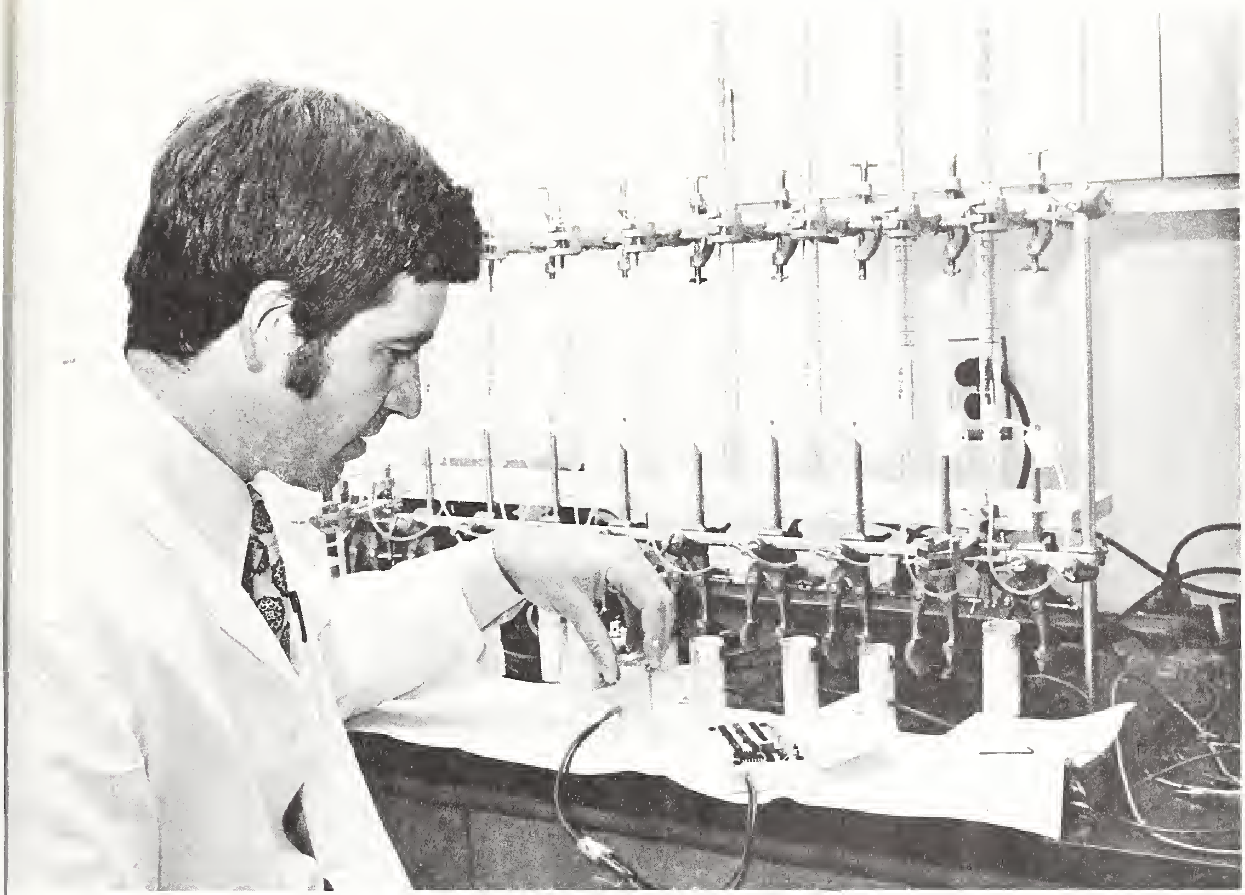
Keiichi Itakura, Ph.D., is in the Division of Biology at the City of Hope National Medical Center, Duarte, Ca. Dr. Itakura and his colleagues conduct research on various aspects of molecular biology including control of gene expression and mechanisms of protein-DNA interactions. (NIH Photo #DP-2)

Boston



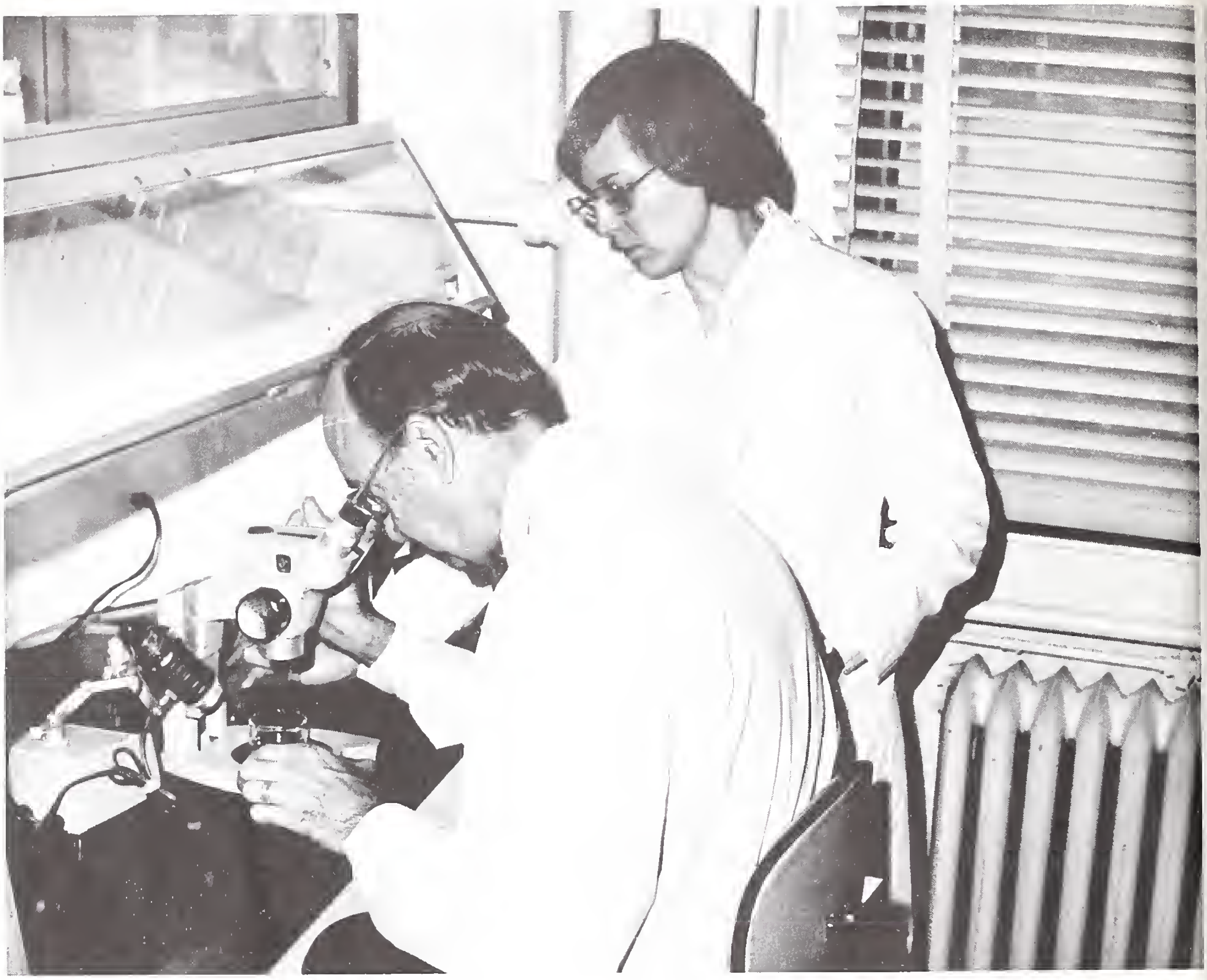
Kenneth H. Gabbay, M.D., is Associate Professor of Pediatrics, Harvard Medica School and Chief of the Diabetes Unit, Children's Hospital Medical Center, Boston. In his laboratory, Dr. Gabbay is studying the biochemistry of diabetic complications. (NIH Photo #DP-3) iabetes

oronto



Michael Albisser, Ph.D., Division of Biomedical Research, Department of Surgery, the Hospital for Sick Children, Toronto, is examining one of ten prototype insulin delivery devices undergoing a 30-day bench test. In his laboratory, Dr. Albisser is studying the pathophysiology of diabetes and how this relates to the development of an artificial endocrine pancreas. (NIH Photo #DP-4)

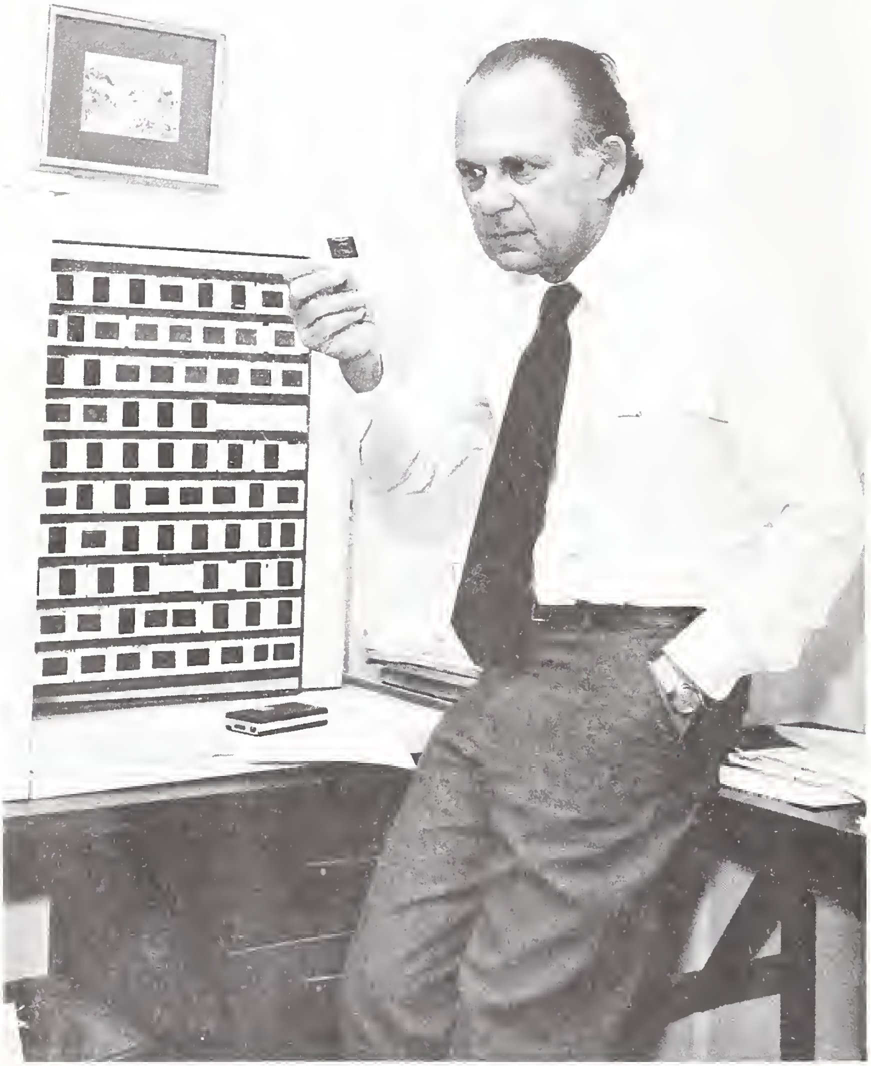
St. Louis



Paul E. Lacy, M.D., is Malinckrodt Professor and Chairman of the Department of Pathology at Washington University School of Medicine, St. Louis. Dr. Lac and his colleagues are studying pancreatic endocrine gland pathophysiology and experimental diabetes, with particular emphasis on pancreatic islet cell growth, function, pathology and transplantation. (NIH Photo #DP-5)

Rex S. Clements, Jr., M.D., is Associate Professor of Medicine, Director of the Clinical Research Center and Assistant Professor of Physiology and Biophysics at the University of Alabama Medical Center, and Director of the Metabolic Research Unit at the Birmingham Veterans Administration Hospital. Dr. Clements is involved in the study of the relationships between abnormal myoinositol metabolism and its phospholipid derivatives and the development of diabetic neuropathy. (NIH Photo #DP-6)

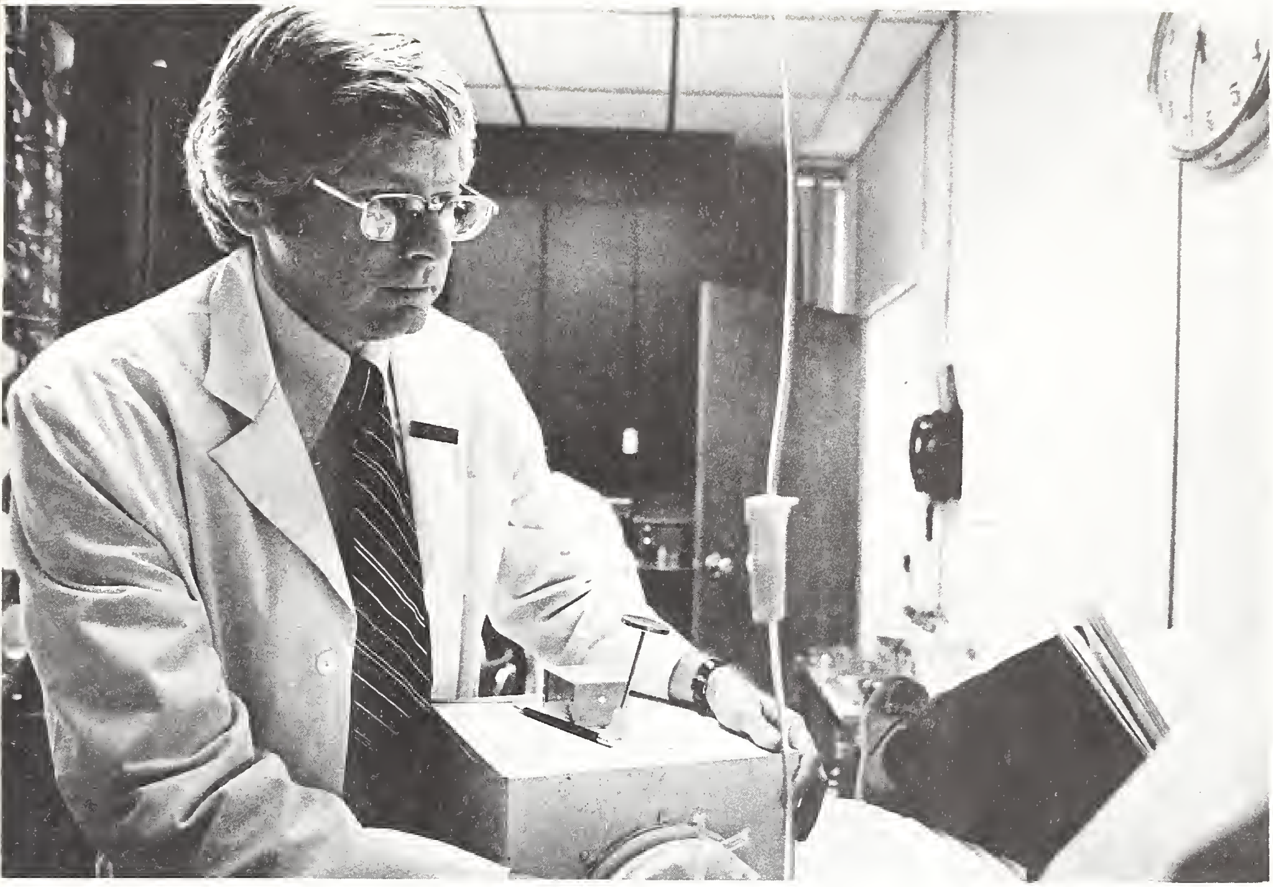
Dallas



Roger H. Unger, M.D., is Professor of Internal Medicine, Department of Internal Medicine at the University of Texas Health Science Center, Southwestern Medical School, Dallas. In his laboratory, Dr. Unger is studying the pathophysiology of diabetes mellitus with particular emphasis on hormonal control of glucose homeostasis. (NIH Photo #DP-7)

Diabetes

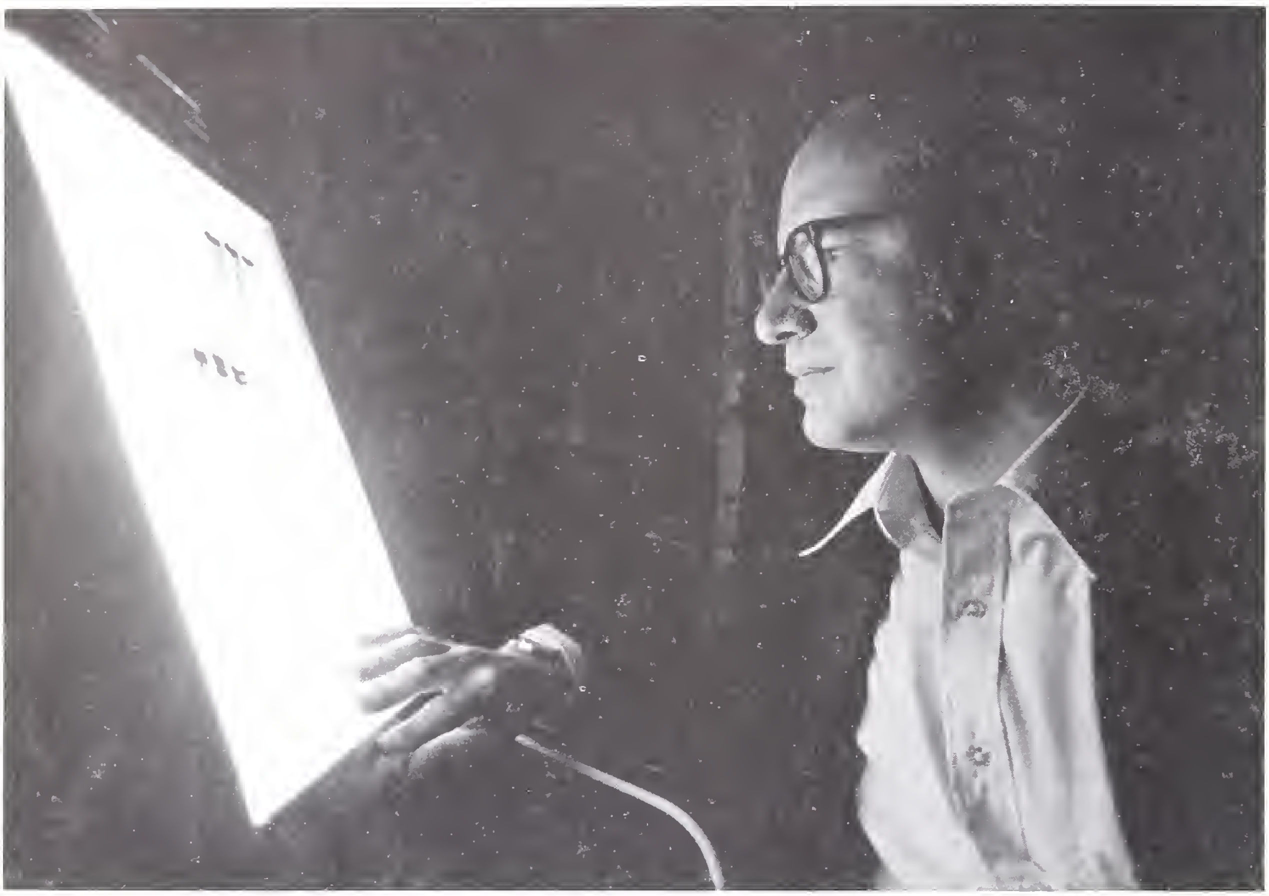
New Haven



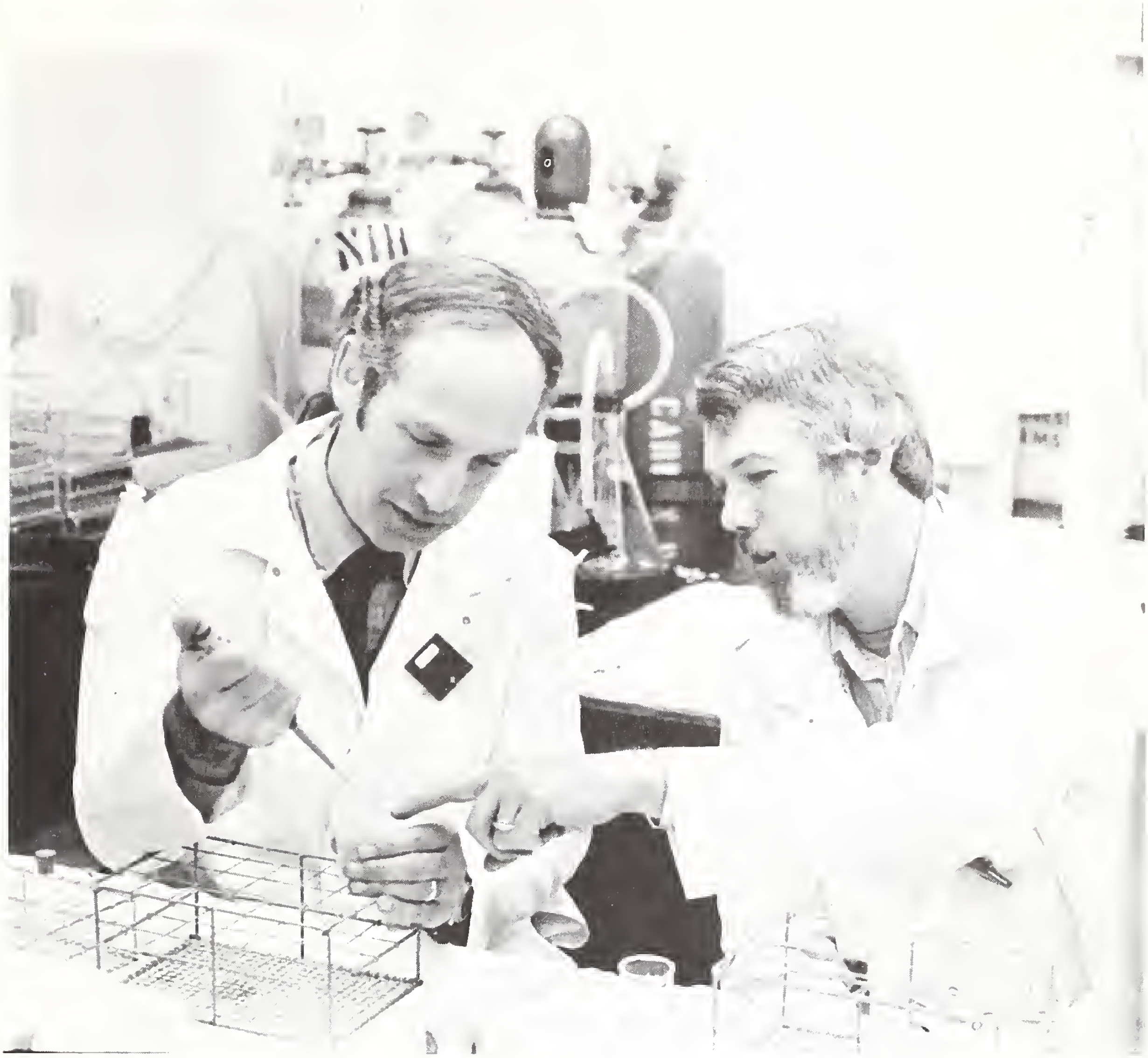
Philip Felig, M.D., is C.N.H. Long Professor and Vice Chairman of the Department of Medicine and Director of the General Clinical Research Center at the Yale University School of Medicine, New Haven. Dr. Felig's group is investigating the regulation of glucose homeostasis, hormone secretion and action, and various clinical aspects of diabetes mellitus and obesity. (NIH Photo #DP-8)

Diabetes

Cambridge



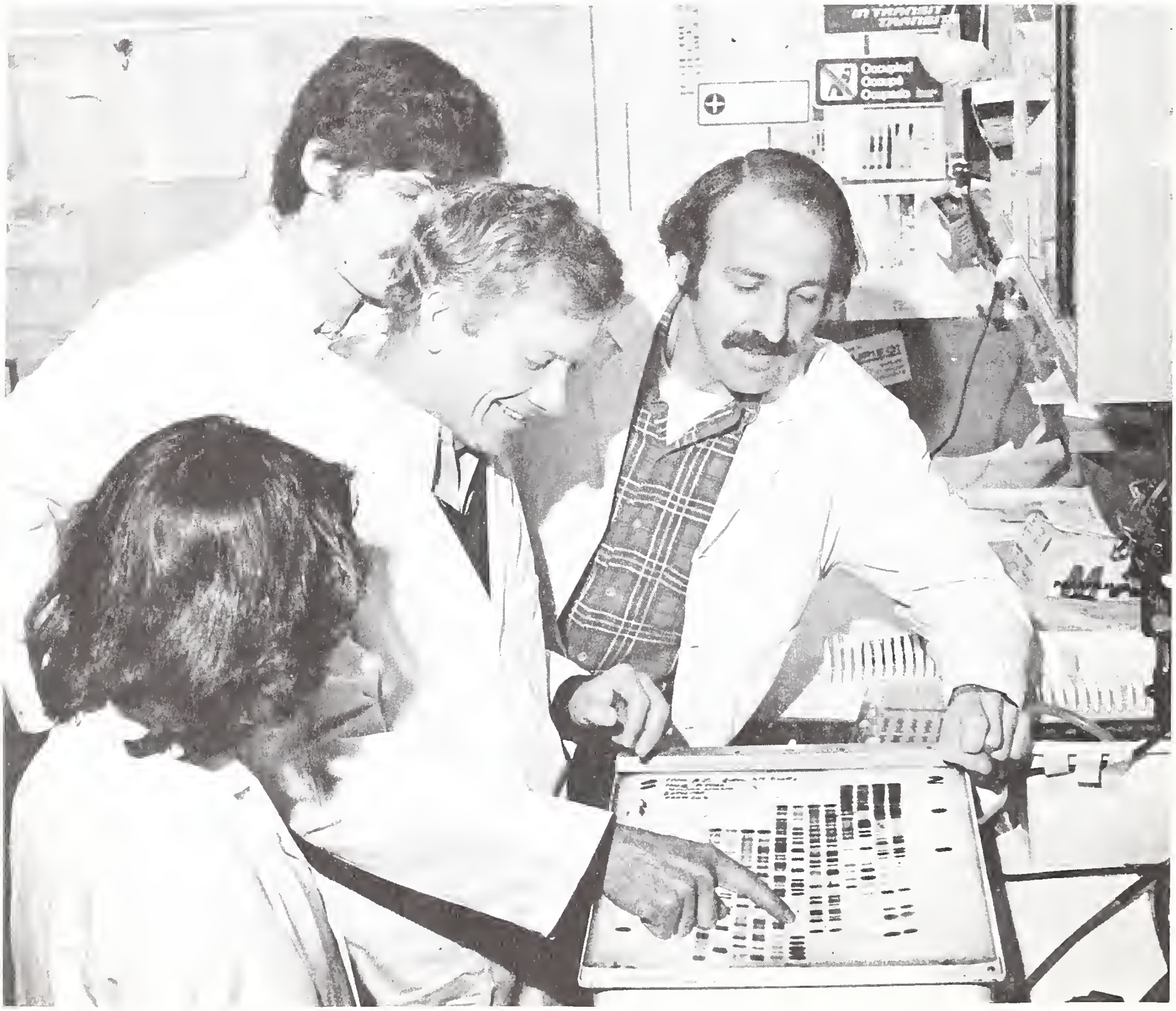
Dr. Walter Gilbert is Professor of Molecular Biology at Harvard University, Cambridge. Dr. Gilbert is studying various aspects of genetic control and mechanisms of protein - DNA interactions including recombinant DNA hormone synthesis. (NIH Photo #DP-9)



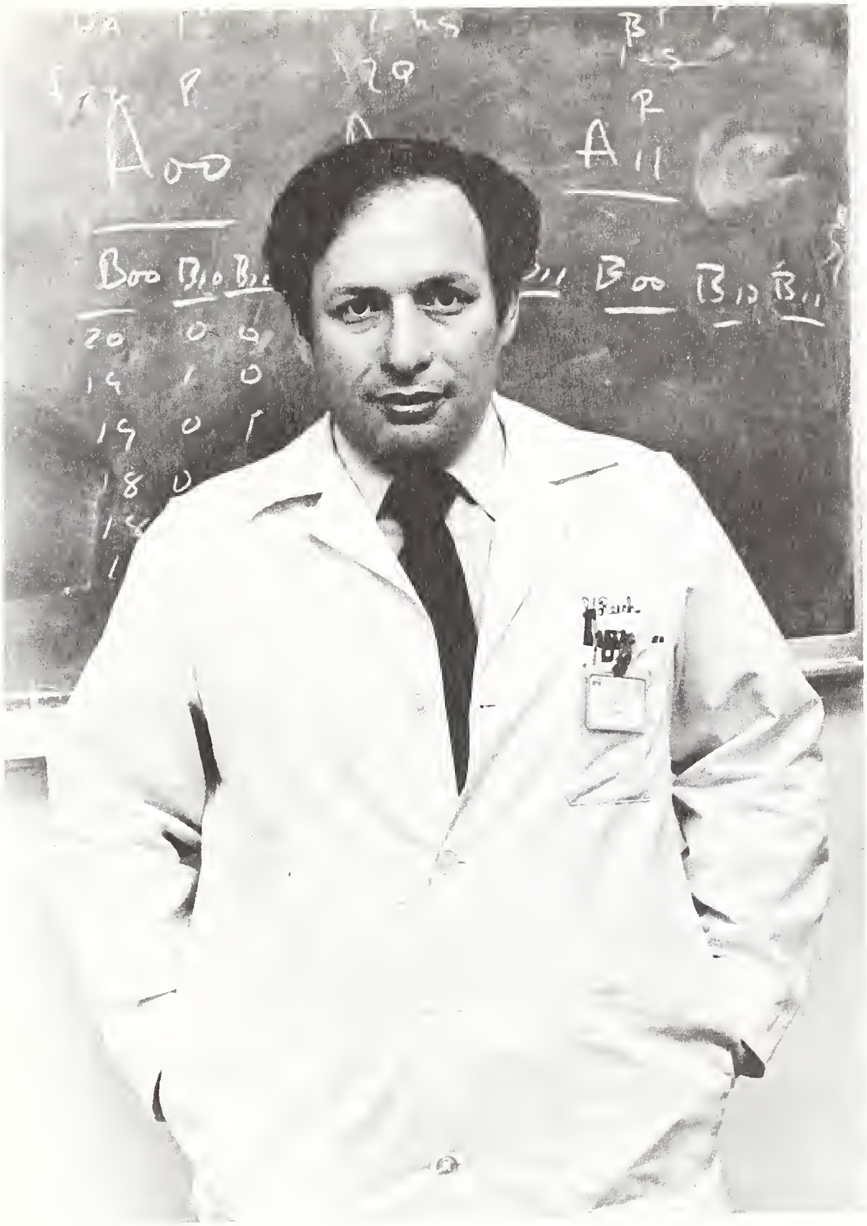
Samuel W. Cushman, Ph.D., (right) is Associate Chief, Laboratory on Cellular Metabolism and Obesity at the National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Md. Lester B. Salans, M.D., (left) Chief of the laboratory, and Dr. Cushman are stydying the mechanisms regulating carbohydrate and lipid metabolism at the cellular and systemic levels under a variety of physiological and pathophysiological metabolic states, especially those related to the mechanism of insulin action. (NIH Photo #DP-10)

Diabetes

San Francisco



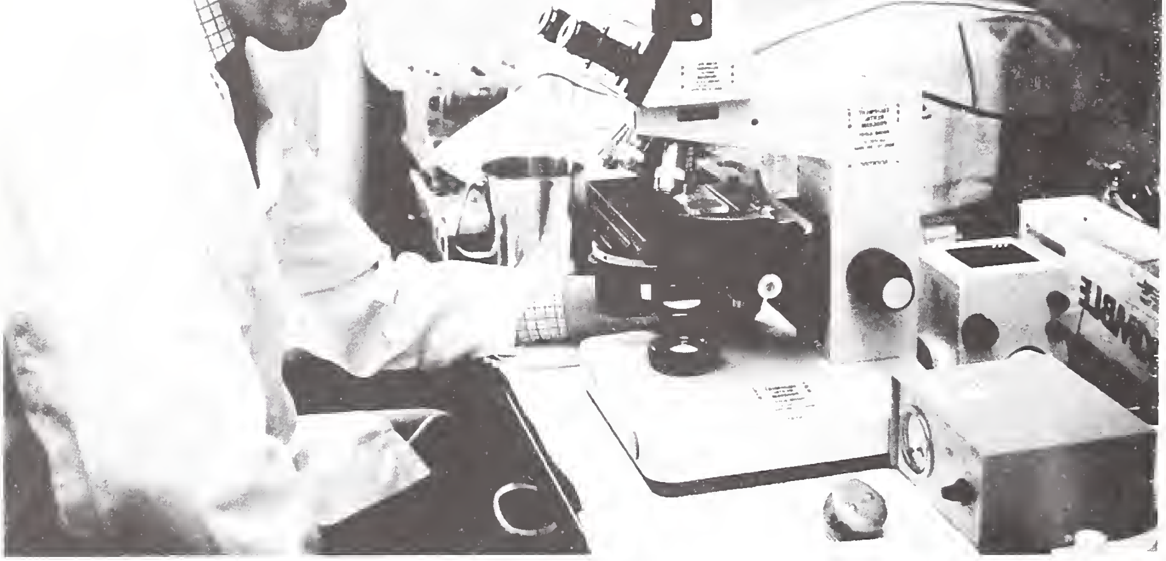
William J. Rutter, Ph.D., is Hertzstein Professor of Biochemistry and Biophysics and Chairman of the Department at the University of California, San Francisco. In his laboratories, Dr. Rutter is studying control of gene expression and mechanisms regulating cytodifferentiation, cell proliferation and enzyme action. (NIH Photo #DP-11)



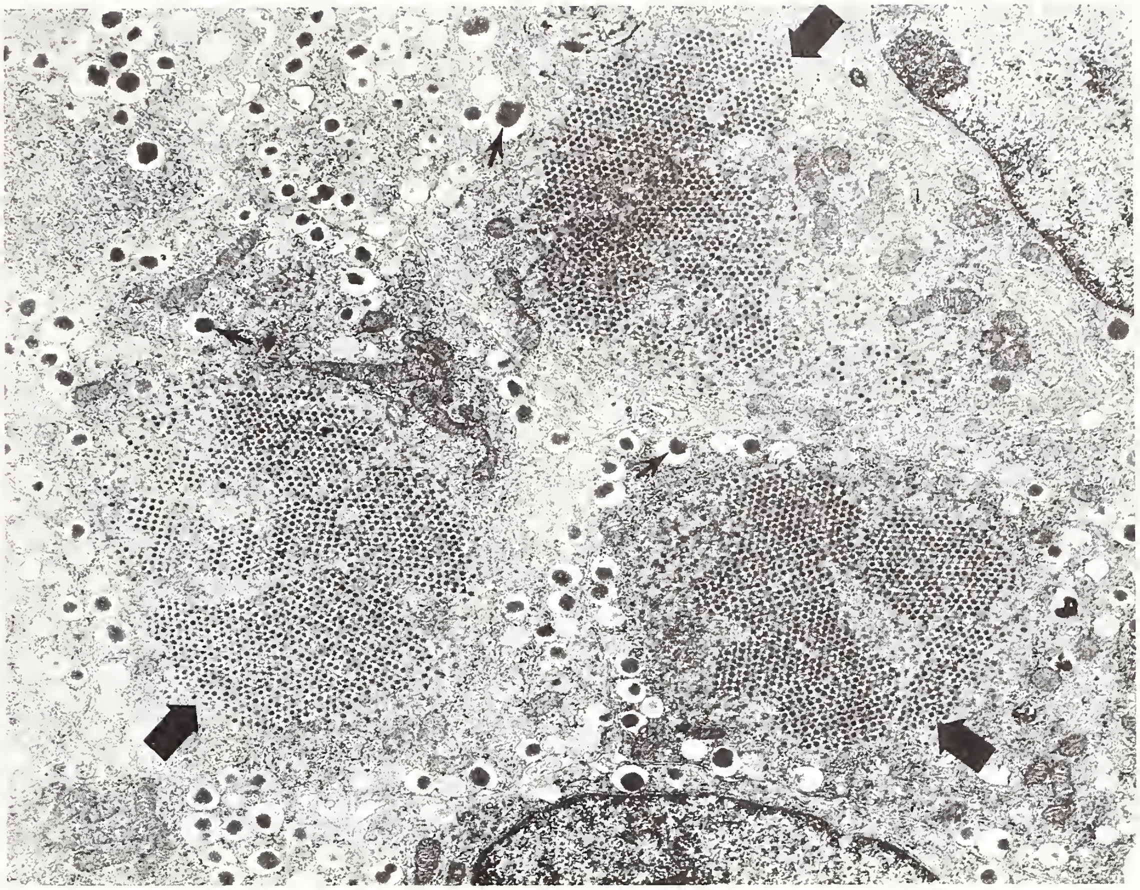
Theodore Reich, M.D., is Professor of Psychiatry and Genetics at the Washington University School of Medicine, St. Louis. Dr. Reich is a population geneticist working on genetics of juvenile diabetes. (NIH Photo #DP-12)

Diabetes

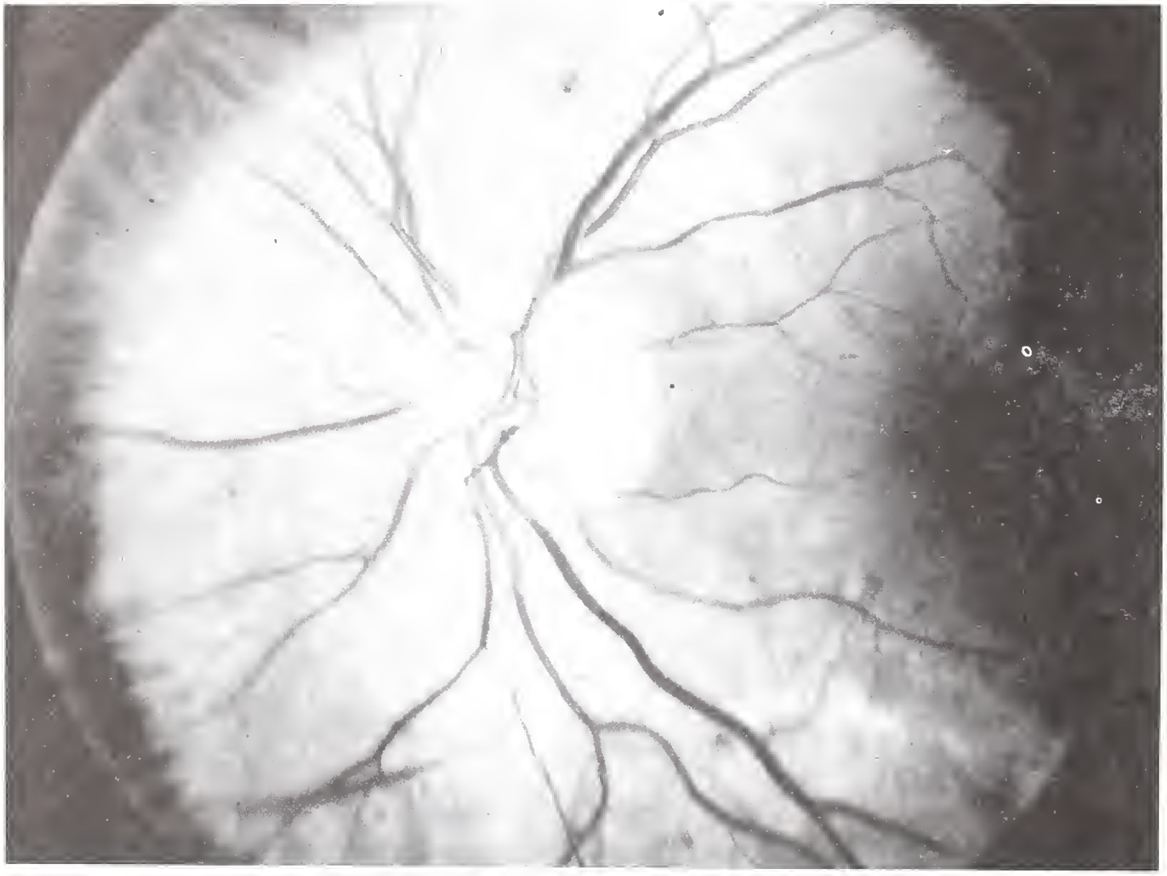
Bethesda



Jesse Roth, M.D., is Chief, Diabetes Branch, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Md. Dr. Roth and his colleagues are studying the pathophysiology of diabetes mellitus with major emphasis on the mechanism of hormone action. The group is one of the leading laboratories in the world conducting research on the specific cell membrane located insulin receptor and on the nature of the insulin-receptor interaction in normal and abnormal conditions such as diabetes mellitus, obesity and states of insulin resistance. (NIH Photo #DP-13



Reoviruses in mice can attack and destroy beta cells in the pancreas producing a diabetes-like syndrome. An electron micrograph (magnification 16,500 times) of a single mouse beta cell showing three crystalline arrays of reovirus indicated by large arrows and vacuoles containing insulin indicated by small arrows. The possible role of viruses as one of the causes of diabetes in both animals and man is being actively investigated. Photo obtained from Dr. Bennett Jenson and Dr. Abner Notkins of the National Institute of Dental Research. (NIH Photo #DP-14)



The fundus photograph of a patient with diabetic retinopathy shows neovascularization--growth of a fine network of abnormal new vessels--directly on the optic disc. Small black dots on the photograph are microaneurysms, while larger blotches are hemorrhages. One example of a hemorrhage in this photo is a black, almost horizontal streak on the lower left. National Eye Institute photograph. (NIH Photo #DP-15)

Editors of publications may request a glossy print of the photographs that appear in this Portfolio.

Ms. Maureen Napper
National Institutes of Health
Building 31, Room 2B-10
Bethesda, Maryland 20014

Ms. Maureen Napper:

Please send me one glossy print of the photograph from the list below:

DP-1 _____
DP-2 _____
DP-3 _____
DP-4 _____
DP-5 _____
DP-6 _____
DP-7 _____
DP-8 _____

DP-9 _____
DP-10 _____
DP-11 _____
DP-12 _____
DP-13 _____
DP-14 _____
DP-15 _____
DP-16 _____

Name: ______________________________
Title: ______________________________
Publication: ______________________________
Address: ______________________________
City, State, Zip: ______________________________
Telephone: ______________________________

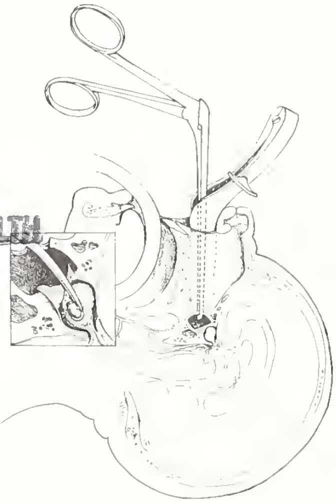
At the Yale Clinical Research Center Dr. Felig chats with a young patient who is wearing a prototype insulin pump on his left side. (NIH Photo #DP-16)

NEWS&FEATURES FROM NIH

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE ■ Public Health Service ■ National Institutes of Health ■ Office of Information ■ Bethesda, Maryland

LIBRARY
OCT 8 [illegible]
NATIONAL INSTITUTES OF HEALTH

AUGUST 1979



See page 9

RESEARCH ADVANCES:

Interferon Found in Patients with Arthritis and Lupus......................1
More Than One Agent May Be Cause for Non-A, Non-B Hepatitis................4
Microsurgical Technique Points to Cause of Acromegaly..................9
Genetic Engineering Produces Human Growth Hormone......................13
Conference Reviews "Natural" Birth Control Methods.............15
Psychiatric Illness Symptoms Found Similar to Thyroid Disease..18
Ground Squirrels Turn Down Thermostat to Save Energy...........21
NINCDS Scientist Finds Food Dye Affects Brain..................24
FIC Announces Fellowships for Sweden, Switzerland, France......25

Thomas H. Flavin, Acting Editor
NIH News Branch
Building 31, Room 2B-10
Bethesda, MD 20205
Phone: (301) 496-1206

NEWS & FEATURES From NIH

August 1979

INTERFERON FOUND IN PATIENTS WITH ARTHRITIS AND LUPUS

Scientists at the National Institutes of Health have found immune interferon in the blood of patients with active autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus (SLE). Because this substance has seldom been detected in healthy persons and now has been shown to disappear during remissions of these conditions, it may be helpful in diagnosing and following autoimmune diseases.

Interferon is a natural defense against viral infections and can modify immune reactions. It is also in the early experimental stages of testing for treatment of certain forms of cancer.

The chief autoimmune diseases are rheumatoid arthritis, SLE, scleroderma and Sjogren's (sicca) syndrome. In these conditions scientists think that patients are sensitized to some of their own proteins and react immunologically against their own organs, sometimes severely enough to damage tissues.

Rheumatoid arthritis inflames and cripples joints in an estimated 5 to 6 million adults in the United States. SLE affects the deeper connective tissues and often the skin, while in Sjogren's disease, secretions of the mouth, eyes, and other regions dry up. Scleroderma, which occurs less often, produces hidebound, thickened skin and severe internal symptoms. In these disorders, symptoms are diverse and develop slowly. All of these diseases occur much more frequently in females than in males. Moreover, patients may have more than one of them at the same time.

Interferon was first recognized over 20 years ago as a soluble substance that prevents viruses from reproducing. However, interferon from one species does not usually protect members of another species. Recently scientists

(more)

showed that there are at least two types of interferon. Type I or "virus-induced" interferon is produced by a wide variety of cells in response to infection. Type II or "immune" interferon is produced by the body's immune cells in response to foreign substances.

For example, earlier work by scientists at the National Institute of Dental Research and others showed that when white blood cells (lymphocytes) from patients with immunity to tuberculosis were incubated with proteins from tuberculosis bacteria, the cells released immune interferon. In contrast, when these tuberculosis proteins were incubated with lymphocytes from individuals without immunity to tuberculosis, interferon was not produced. Researchers can differentiate between immune and virus-induced interferon by the sensitivity of immune interferon to treatment with acid.

The fact that interferon also could be produced in experimental animals on an immune-specific basis suggested to the NIH scientists that interferon might be produced in patients with diseases involving an autoimmune response. Further, recent studies have shown that interferon can alter immune responses in animals. Many, but not all of these alterations occur in patients with SLE. For example, lupus patients have increased antibody levels, decreased cell-mediated immune responses and kidney disease.

Hence the investigators looked for and found immune interferon in the blood of patients with autoimmune diseases. They detected this interferon in the blood of 46 percent of patients with SLE, 50 percent of patients with rheumatoid arthritis, 60 percent of patients with scleroderma, and 27 percent

(more)

INTERFERON (CONT'D)

of patients with Sjogren's disease. In contrast, less than 3 percent of normal individuals had significant levels of immune interferon in their blood.

Because patients with SLE have flare-ups and remissions, these patients were separated into groups with and without active disease and retested for interferon. The scientists found immune interferon in the blood of 71 percent of patients with active SLE but in only 21 percent of those in remission. Patients with SLE, followed over many months, also showed rises and falls in levels of immune interferon as the disease waxed and waned. Interferon was usually absent when patients were symptom-free. These studies suggest that detection of interferon may be helpful in diagnosing and monitoring disease activity.

The investigators do not believe that interferon causes SLE but wonder whether it might contribute to some of the pathologic changes.

The presence of interferon in the blood of patients with autoimmune diseases raises a number of questions. Because the antiviral activity of interferon is well established, the scientists speculate that the production of interferon may protect the patient suffering from autoimmune disease from contracting other (e.g. viral) diseases. They are presently investigating the possibility that immune interferon may be found in the circulation of patients with a variety of immunological disorders.

The studies by J. Hooks, H.M. Moutsopolous, S.A. Geis, and A.L. Notkins of the National Institute of Dental Research and N.I. Stahl and J.L. Decker of the National Institute of Arthritis, Metabolism and Digestive Diseases were reported in the July 5 issue of the *New England Journal of Medicine.*

###

NEWS & FEATURES From NIH

August 1979

MORE THAN ONE AGENT MAY CAUSE NON-A, NON-B HEPATITIS

A team of NIH researchers has reported specific visual evidence that a major type of viral hepatitis--known as non-A, non-B hepatitis--may be caused by more than one agent.

The evidence comes out of electron microscopic observations of liver cells from chimpanzees experimentally infected with non-A, non-B hepatitis. According to the researchers, their findings may be an important step in developing methods for diagnosing this disease in man.

Non-A, non-B hepatitis is a newly recognized form of viral hepatitis. It is believed to be responsible for as much as 90 percent of hepatitis resulting from blood transfusions. Hepatitis B has been mostly eliminated by screening blood before transfusion and rejecting blood from infected donors. According to some estimates, about seven to ten percent of the three million people who receive blood transfusions each year in the United States will develop post-transfusion hepatitis. Although one or more viruses are suspected, the causative agents of non-A, non-B hepatitis are as yet unidentified.

Since screening tests are not available, a diagnosis of non-A, non-B hepatitis is made by excluding other known causes of viral hepatitis, such as the more commonly recognized hepatitis types A and B viruses, for which tests have been developed in recent years. Efforts to identify markers of non-A, non-B hepatitis have been unsuccessful. However, several groups of investigators have been able to transmit the infection to chimpanzees using the blood of infected humans. This not only provided a suitable animal model for studying non-A, non-B hepatitis, but also implicated an infectious, transmissible agent or agents.

(more)

HEPATITIS (CONT'D)

Attempting to identify and characterize more specifically the elusive non-A, non-B agents, the NIH scientists inoculated chimpanzees with potentially infectious material, originally derived from the blood of patients with hepatitis not caused by the hepatitis A or B viruses. Two strains were selected because they had been known to produce hepatitis infection and the illnesses they produced had distinguishing characteristics, suggesting two different agents.

Each chimp received one of the two strains--designated as F and H. The inoculated animals were then tested for hepatitis infection and liver biopsies were taken and prepared for electron microscopy.

Examining the biopsies, the investigators noticed two different structural changes in the liver cells of the infected chimps. Tubular-like structures appeared in the livers of chimps infected with strain F. These structures occurred only during the acute phase of the illness, suggesting a direct association with infection. Interestingly enough, they were not observed in the chimps that received strain H. Liver cells from these animals displayed nuclear abnormalities and clusters of particles which were not obviously virus-like.

The scientists believe that these liver changes are characteristic of non-A, non-B hepatitis infection. All non-A, non-B infected chimps in the study developed one or the other structure, but none of the animals developed both. In addition, the tubular structures were seen only in association with strain F, while the nuclear particles, only with strain H. Furthermore, neither structure was detected in chimps infected with the A or B hepatitis viruses, which produce distinguishing liver changes of their own.

(more)

HEPATITIS (CONT'D)

On a cautious note, the investigators add that the precise relationship of the two structures to the suspected non-A, non-B hepatitis agents in unknown. Further tests and observations are needed to determine the association.

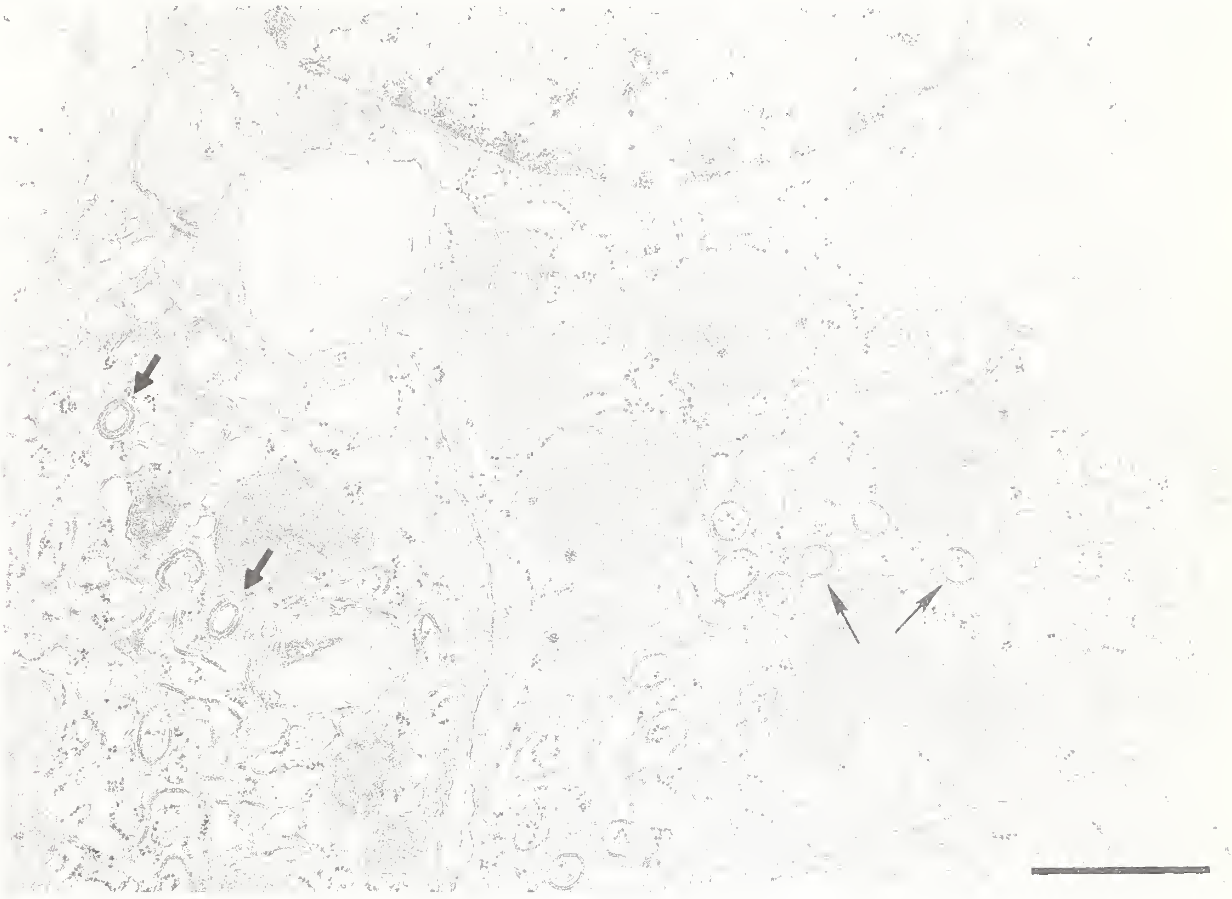
For now, the scientists believe that the liver changes are an experimental aid to the diagnosis of non-A, non-B hepatitis in chimpanzees. If more evidence is obtained establishing a link between the two, the structures may be useful in developing practical methods of diagnosis and in screening for carriers.

Previous investigations of patients with multiple attacks of non-A, non-B hepatitis led scientists to speculate that there is more than one non-A, non-B hepatitis agent. These individuals showed marked clinical and serologic variability with each infection. Although there is probably more than one non-A, non-B hepatitis agent, the investigators are hopeful that, based on the results of this study, the number of non-A, non-B hepatitis agents will be small.

The report of this research by Yohko K. Shimzu, Stephen M. Feinstone and Robert H. Purcell from the National Institute of Allergy and Infectious Diseases, Harvey J. Alter from the Clinical Center Blood Bank and William T. London from the National Institute of Neurological and Communicative Disorders and Stroke, appeared in the July 13, 1979 issue of *Science* magazine.

(more)

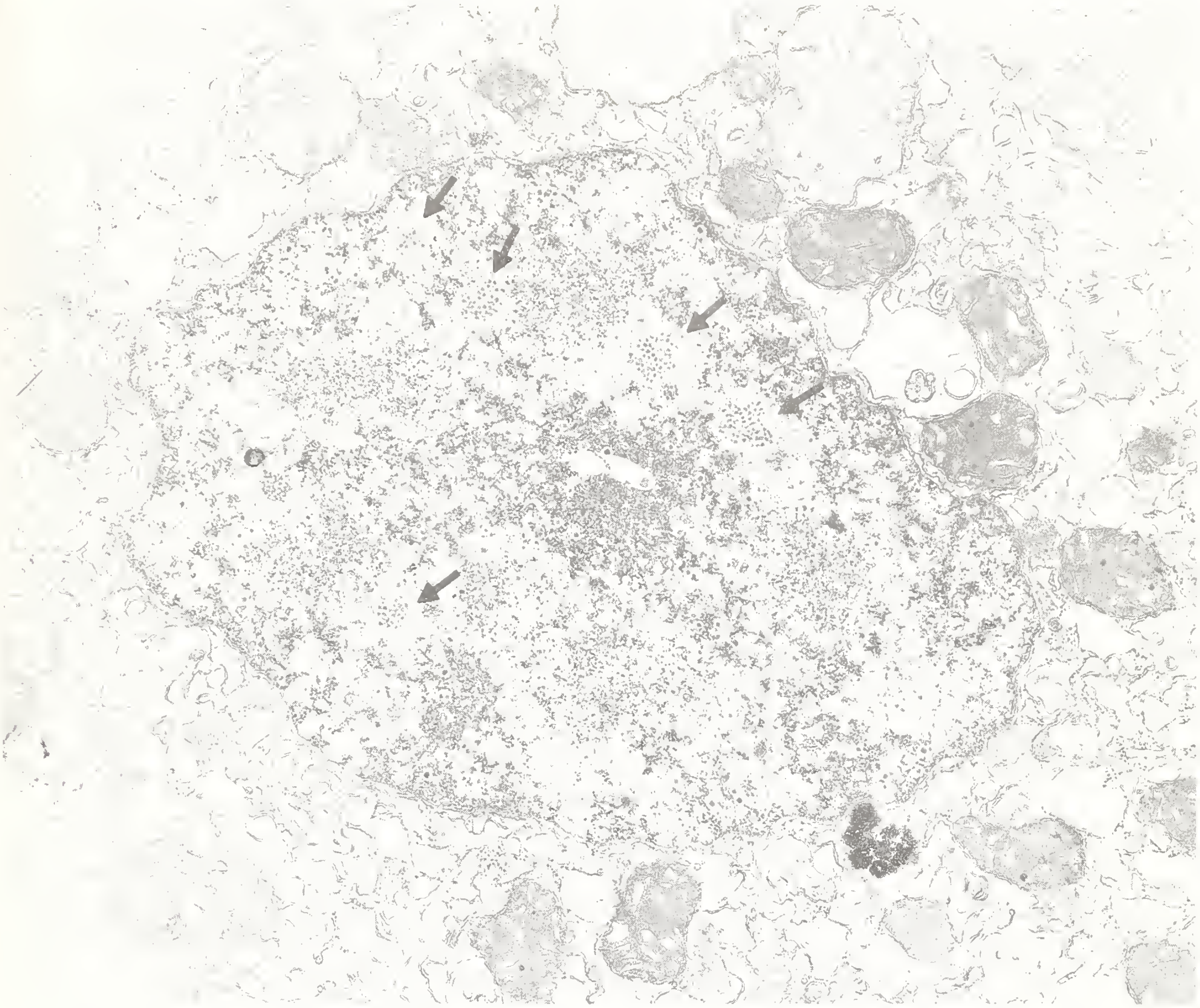
HEPATITIS (CONT'D)



This electron micrograph of liver cells from a chimpanzee with non-A, non-B hepatitis (strain F) reveals circular structures in the cytoplasm, not observed in the chimps infected with the hepatitis A or B viruses. Occasionally, the structures were double-walled. (NIH Photo #1624)

(more)

HEPATITIS (CONT'D)



Distinct nuclear changes in liver cells from chimpanzees with non-A, non-B hepatitis (strain H) can be seen in this electron micrograph. Most striking is the appearance of clusters of particles. (NIH Photo #1625)

###

MICROSURGICAL TECHNIQUE POINTS TO CAUSE OF ACROMEGALY

By Wendy K. Bowis, a senior at
Wellesley College, Massachusetts

Acromegaly, the disease caused by the hypersecretion of the pituitary growth hormone (HGH) and characterized by the grotesque overgrowth of the body's extremities, has puzzled scientists for decades because of the uncertainty of its origin. Because the pituitary is regulated by the hypothalamus, the HGH elevation could be caused either by abnormal signals from the hypothalamus, or by abnormal responses of pituitary cells to these signals.

Researchers from the Departments of Medicine and Neurological Surgery at the University of Pittsburgh School of Medicine have introduced microsurgery as a new treatment of the disease as well as a possible key to understanding its cause. Their findings suggest that acromegaly is due to a disturbance of the pituitary itself. This research was supported in part by NIH's Division of Research Resources at the Clinical Research Unit of the University of Pittsburgh.

The patient studied was a 54-year-old woman with many skeletal manifestations of acromegaly. She exhibited a marked increase in glove and ring size and an increase in her shoe size from 4B to 8B. A broad nose, enlarged feet and thyroid were also noted.

The experiment was based on the surgical removal of a pituitary tumor, leaving the remaining normal HGH-secreting cells and the hypothalamic-pituitary connection intact. Responses to stimulation and suppression tests that are thought to alter HGH secretion via the hypothalamus were evaluated before and after surgery, providing a clue to which element of the system is defective in the disorder.

(more)

ACROMEGALY (CONT'D)

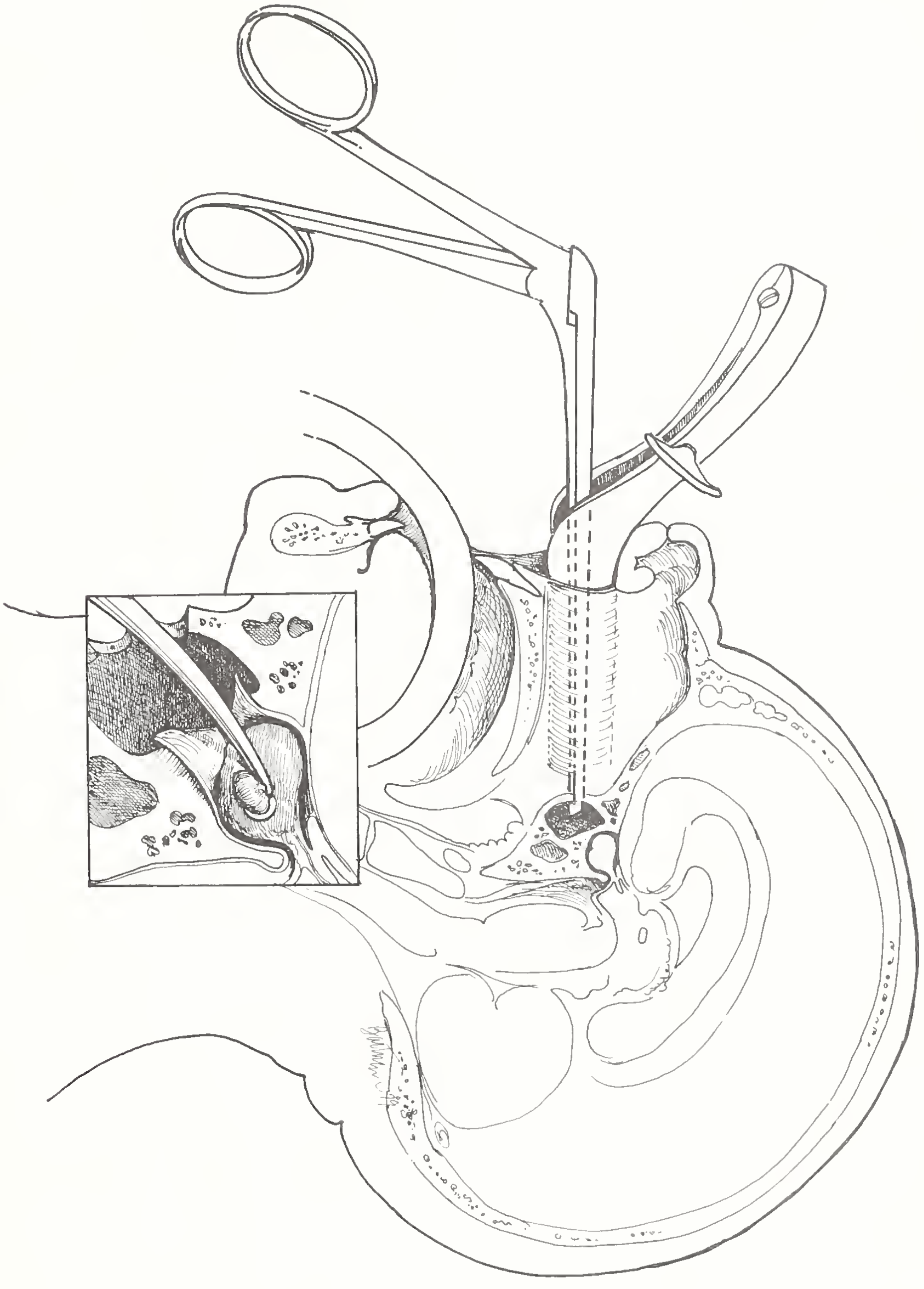
The stimulation and suppression tests included a glucose tolerance test and a combined arginine-insulin test. These tests induce metabolic conditions such as glucose loading or hypoglycemia, under which the hypothalamus would normally respond by altering the secretion of HGH. In fact, the growth-promoting activity of HGH is thought to be a result of its function as an overall regulator of many metabolic processes. For example, radioimmunoassay studies have confirmed that the normal release of HGH into the blood stream is promptly stimulated by a fall in blood sugar levels.

Prior to surgery, the patient showed abnormal responses to the changing metabolic conditions induced by the tests. The rising blood sugar brought on during the glucose tolerance test stimulated an elevation of basal HGH from 18 ng/ml to 50 ng/ml.* The normal response is a depression of HGH to less than one ng/ml. The arginine infusion caused a transient decrease in HGH from 16 ng/ml to 11 ng/ml, while during insulin-induced hypoglycemia, the HGH level fell to the low value of 4 ng/ml. Arginine, through its role as an essential amino acid, as well as insulin, would normally stimulate HGH secretion to greater than 7 ng/ml.

The surgical technique involved was transsphenoidal, enabling the pituitary to be reached from the sphinoid sinus through an oronasal approach. After elevating the nasal membrane and inserting a bivalve speculum, the sphenoid floor is opened with grasping forceps. A microcurette can then enter the sella to extract the adenoma. (See illustration). A television monitor verifies the

* One nanogram (ng) is equal to one billionth of a gram; a milliliter (ml) is equal to one thousandth of a liter.

(more)



(more)

A cutaway view of transsphenoidectomy which reaches the pituitary from the sphenoid sinus through an oronasal approach. After elevating the nasal membrane and inserting a bivalve speculum, the sphenoid floor is opened with grasping forceps. The enlargement shows the microcurette entering the sella to extract the adenoma. (NIH Photo #1626)

****

This research was conducted by Drs. Z. Joseph Wanski, Alan G. Robinson, and Peter J. Jannetta from the Departments of Medicine and Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania. The article appeared in *Metabolism*, Vol. 28, No. 6, June 1979.

NIH LIBRARY

location of surgical instruments.

After the removal of a small tumor from the left side of the pituitary, the patient's HGH dynamics were dramatically different. The elevated blood sugar during the glucose tolerance test did not cause an elevation of HGH as had been seen before surgery. The insulin tolerance test now showed a stimulation, rather than reduction, of HGH by the hypoglycemia, with a peak HGH level of 8 ng/ml. By one year postoperatively, a glucose-tolerance test demonstrated a fasting HGH of 1 ng/ml, and both arginine infusion and insulin hypoglycemia caused an even greater stimulation of HGH.

In addition to the metabolic improvements seen after the removal of the tumor, the acral effects on the extremities also showed improvement. By two months postoperatively, the patient noticed a decrease in the soft tissue of her hands.

It appears that through surgery, the source of the malfunction was removed. The postoperative tests demonstrated HGH secretion in response to low blood sugar and inhibition in response to high blood sugar levels. This is the normal paradoxical response of HGH to changes in blood sugar content. The tumor, then, represented some abnormal physiology of the HGH-secreting cells of the pituitary, while normal hypothalamic control of HGH secretion remained.

Microsurgery, with total removal of the pituitary tumor in acromegaly, therefore, not only points to a possible etiology of the disease, but may provide a complete cure as well. While various forms of radiation are also effective treatment methods, surgery may be most appropriate for small tumors where a complete cure can be obtained and where pituitary function can be preserved.

###

GENETIC ENGINEERING PRODUCES HUMAN GROWTH HORMONE

Using genetic engineering techniques, scientists at the University of California in San Francisco have taken a major step toward the mass production of a carbon copy of human growth hormone (HGH), also called somatotropin.

NIH's National Institute of Arthritis, Metabolism, and Digestive Diseases grantees Drs. John Baxter, Howard Goodman and associates recently induced bacteria to synthesize the large, complex molecule of the hormone which is essential to the achievement of normal stature. One of the first practical spin-offs of recombinant-DNA research, the procedure holds potential for the delivery of adequate supplies of HGH for both clinical treatment of hypopituitary dwarfism as well as basic research. A similar synthesis was recently reported by Genentech, Inc., a private biochemical firm in Palo Alto, California.

Using the natural growth hormone gene, the investigators attached this genetic blueprint to bacterial molecules called plasmids--messenger rings of DNA inside bacteria. Loaded with their new biochemical instructions, the plasmids were inserted into strains of the common laboratory bacteria, *Escherichia coli*.

The living factories began to manufacture HGH molecules as programmed by their genetic machinery. While radioimmunoassay assured the final product's authenticity, its biological activity has yet to be verified for its identity to the natural hormone. This information is essential in that any alteration in the growth hormone molecule could render it ineffective or capable of inducing undesirable side effects.

Recognized from antiquity, dwarfism has been described in the science, art and literature of ancient civilizations. It was not until 1908, however, that the relationship between pituitary gland dysfunction and one type of dwarfism

(more)

HORMONE (CONT'D)

was identified. Fifty years later, successful growth stimulation was achieved in a hypopituitary child using hormone derived from human pituitary glands taken at autopsy that had been collected and stored in acetone. This accomplishment signalled a new era in endocrinology.

At present, human pituitary glands removed at autopsy provide the only source of HGH. Because at least 120 pituitaries per year are required to provide sufficient hormone to treat each child, supplies of this important material are generally limited.

To increase the availability of growth hormone, the National Pituitary Agency (NPA) was established in 1963 under contract to the NIAMDD. This agency collects pituitary glands from hospitals and medical centers across the country, and organizes the extraction and distribution of HGH for use in clinical growth research studies.

In previous research, Drs. Baxter and Goodman successfully manufactured rat growth hormone using recombinant-DNA techniques. This achievement demonstrated that alterations in the message-coding plasmid and its subsequent implantation into bacteria could eventually produce numerous proteins essential to the correction of a variety of human diseases.

In addition to human growth hormone, other likely targets for future genetic engineering might include thyroid hormone, hormones that stimulate red cell production and nerve growth, enzymes for industrial use, and a host of other materials. Should the synthetic HGH demonstrate bioactivity--the ability to function in the body identically to the natural hormone--the substance may become commercially available in the not too distant future.

###

NEWS & FEATURES From NIH

August 1979

CONFERENCE REVIEWS "NATURAL" BIRTH CONTROL METHODS

Natural family planning (NFP)--fertility regulating methods that depend on the ability of a couple to identify the woman's fertile period and then practice sexual abstinence during this period if the intent is to limit or space family size--was the focus of a recent international meeting of scientists and teachers.

The workshop was sponsored jointly by the National Institute of Child Health and Human Development (NICHD), the Bureau of Community Health Services, the International Federation for Family Life Promotion, the Human Life and Natural Family Planning Foundation, and the World Health Organization. Some 70 participants from six nations attended the 2½-day meeting, June 27-29, at the Linden Hill Hotel in Bethesda.

Dr. Irvin Cushner, DHEW Deputy Secretary for Population Affairs, opened the meeting. He noted that there has been an increased demand for natural family planning methods. He attributed this increased demand to three groups; a group motivated by personal beliefs, a group concerned about the safety of other methods of birth control such as the Pill or IUD, and those motivated by a general move toward naturalness in all aspects of health care.

The newer NFP methods that are currently promoted replace the now obsolete "rhythm" or "calendar" methods of birth control. Little research has been done in the NFP field, and a major purpose of the Bethesda meeting was to discuss priorities for research and service.

Information on NFP is important to DHEW because Title X of the Public Health Service Act mandates that natural family planning methods be among those offered by HEW-sponsored family planning programs.

(more)

One recommendation coming out of the meeting was that a national NFP steering committee be organized. This committee, according to its sponsors, would analyze the current status of NFP providers and users. It would identify problems and needs related to the development of a coordinated, high-quality NFP research and service delivery system.

Among the research needs identified at the workshop were additional studies on the basic biology of human reproduction and on psycho-social factors in NFP practice. With information now available, the theoretical effectiveness of NFP methods approaches 98 to 99 percent. But in practice, the effectiveness rate is often much lower. NFP advocates differentiate between two types of failures--method failures, instances where the technique fails, and user failures, where couples risk coitus on days when fertility is probable. Rates of user failure are generally much higher than rates of method failure.

Understanding why couples take risks in family planning, the psychological effects of abstinence, and the motivation of users of NFP are important questions to be answered by psycho-social research.

One highlight of the meeting was the presentation of results from several studies comparing the use-effectiveness of the two most widely used NFP methods--the ovulation method (OM) or the sympto-thermal (ST) method. With the OM method, the woman learns to detect her fertile period by recognizing changes in the quantity and characteristics of her cervical mucus. The ST method requires the woman to monitor other bodily symptoms, primarily changes in her basal body temperature, in addition to cervical mucus, to identify ovulation. Both methods have their advocates in the NFP community, but few well designed studies have

(more)

been done that quantify the effectiveness of either method.

One study reported at the meeting was conducted in the Los Angeles area and supported by the NICHD. Dr. Maclyn Wade, study director, reported that drop-out rates and pregnancy rates were higher for OM than for ST. He said that in the LA study there was a 2½-to 3-fold difference in pregnancy rate between the two methods. Similar data were presented by Dr. Hanna Klaus from a multicenter study conducted in Kansas, Missouri and Minnesota.

Another study sponsored by WHO was conducted in Columbia, South America. Similar in design to the LA study, the South American study did not find statistically significant differences in the drop-out rates (56 percent for OM users and 48 percent for ST users) nor in the pregnancy rates (23.6 percent for OM users and 18.2 percent for ST users) between the two methods.

###

PSYCHIATRIC ILLNESS SYMPTOMS FOUND SIMILAR TO THYROID DISEASE

Some patients exhibiting the abnormal signs and symptoms of psychiatric illness may be misdiagnosed. The thyroid function test is particularly important in screening psychiatric patients because the symptoms of thyroid disease are often dismissed as manifestations of a psychiatric illness.

Thyroid function tests were routinely performed on 480 male and female patients (ranging in age from 11 to 87 years) who were admitted to the psychiatric evaluation unit of the Yale-New Haven Hospital. During the two-year study the researchers found abnormal results in evaluating constant and transient changes in circulating thyroid hormone levels. Those patients with abnormal test results were repeatedly tested on a weekly basis until their thyroid hormone values returned to normal or the diagnosis of hypertension or hypothyroidism was established.

The levels of serum total thyroxine (TT$_4$) and thyroxine-binding capacity (T$_4$BC) were both measured. These two results enabled the researchers to determine the estimated free thyroxine (EFT$_4$), which closely reflects the measured free thyroxine (FT$_4$) levels. Thyroxine is a hormone secreted by the thyroid gland which maintains a normal level of metabolism within the cells of the body. It aids the cells in their uptake of oxygen and helps regulate the metabolic rate in the body. They also measured the thyroid-stimulating hormone (TSH), a hormone secreted by the anterior lobe of the pituitary gland that stimulates the growth of the thyroid gland and secretion of thyroxine.

Abnormalities in values of total thyroxine (TT$_4$) and T$_4$BC (thyroxine-binding capacity) were common in this group of psychiatric patients. Most of these alterations were of little or no physiological or clinical importance, in that

(more)

THYROID (CONT'D)

simultaneous changes in values of TT_4 and T_4BC resulted in a normal level of EFT_4 (estimated free thyroxine). However, the level of EFT_4 was abnormal in 18 percent of the entire group.

The EFT_4 level was elevated in 43 (9 percent) of the patients. In 27, it spontaneously reverted to normal. Elevated EFT_4 levels would suggest hyperthyroidism. Transient elevations of EFT_4 levels have been reported to occur in various acute and chronic organic illnesses; these observations can thus be extended to acute psychiatric illnesses.

The levels of EFT_4 was decreased in 42 (9 percent) of the patients, suggesting hypothyroidism, and 16 spontaneously returned to normal levels. Transient depression of the EFT_4 levels may represent a stress-induced or alcohol-induced effect on thyroid hormone distribution and metabolism or on the hypothalamic-pituitary axis. Secondary hypothyroidism was diagnosed in eight patients.

These test results are higher than those found in a general hospital setting and much higher than that reported for incidence in the general population.

Only one patient had a persistent elevation of EFT_4, which was eventually diagnosed as iodine-induced hyperthyroidism. The clinical signs of hyperthyoidism were: 1) a fine tremor; 2) smooth, moist skin, 3) rapid heart beat, and 4) lid lag. Some of these signs had originally been attributed to the patients' agitated state. There was also one case of hypothyroidism induced by lithium treatment.

In conclusion, the thyroid function test is important in examining psychiatric patients because the symptoms of thyroid disease are often dismissed as manifestations of a psychiatric illness. Patients with known thyroid disease may be receiving inadequate or excessive replacement therapy. Also, drugs given for

(more)

treatment of mental states, particularly lithium and phenytoin, may induce alterations in thyroid function. Therefore, a detailed history of thyroid dysfunction or therapy appears to be essential in forming any psychiatric evaluation.

This research was conducted by Drs. Kenneth L. Cohen and Mary E. Swigar from the Departments of Medicine (Dr. Cohen) and Psychiatry (Dr. Swigar), Yale-New Haven Hospital, and the West Haven Veterans Administration Hospital, West Haven, Connecticut. It was supported in part by a training grant from the National Institute of Arthritis, Metabolism, and Digestive Diseases and appeared in the July 20, 1979 issue of the *Journal of the American Medical Association.*

###

NEWS & FEATURES From NIH

August 1979

GROUND SQUIRRELS TURN DOWN THERMOSTAT TO SAVE ENERGY

By Joyce F. McCarthy

Conserving energy appears to be a natural instinct for Mother Nature. Turning down the biological thermostat in warm-blooded animals is achieved by hibernation and estivation. The ground squirrels reported on in this study were able to reduce their metabolic rate by at least one half through a 10° lowering of body temperature during shallow torpor. In effect, this is equivalent to doubling your miles per gallon or, in this case, per calorie.

Hibernation, the dormant state in which certain animals pass the winter, is characterized by a state of reduced metabolism, muscle relaxation, and slow wave sleep. The sympathetic nervous system accomplishes a regulated resetting of the usual body reactions of the organism. However, estivation, the modifications made by an animal to survive a hungry, hot, dry summer, seems to occur without being triggered by outside heat but rather in response to food deprivation. This study found that estivation and hibernation are corresponding physiological processes.

Hibernation habits were studied in one baby and three adult male, round-tailed, desert ground squirrels. Each animal was housed inside a 10"x10"x17" wooden box with cotton nesting material inside a wire cage. The animals were maintained in an electrically shielded incubator with 12 hours of light and 12 hours of darkness.

A tube was inserted 3mm below the outermost membrane of the head which covers the brain and spinal cord. The tube measured brain temperature, and permanent electrodes were implanted to record brain, eye, muscle and heart activity in each squirrel.

(more)

SQUIRRELS (CONT'D)

The study found that shallow torpor was induced in the squirrels by food deprivation characterized by almost continuous sleep. The point of entry into torpor was defined as that point in which body temperature progressively declined below 32°C (89.9°F).

The four animals first entered torpor after 2, 3, 5 and 19 days of food deprivation. Subsequent periods followed at approximately 24 or 48 hour intervals. A distinct nocturnal pattern of torpor occuring at the usual sleep time was present in three of the squirrels. During the first half of the night, body temperature decreased by 1°C (33.8°F) every 40-50 minutes; it stabilized at 26°- 28°C (78.8°- 82.4°F) for 1-4 hours (reaching a maximum temperature drop of 11.1°), and then increased to normal temperatures over a period of about one hour. Torpor periods lasted an average of about 10 hours. The return to normal body temperatures was spontaneous and occurred during the last two hours of darkness (6-8 a.m.).

Heart rate, an index of both arousal and metabolic rate, was found to be 84 percent lower during torpor than during wakefulness. Sleep time was significantly increased during torpor than during preceding normal temperatures. Slow wave sleep also increased during torpor, but there was a dramatic reduction in the amount of time spent in REM sleep.

At the lowest body temperatures of 26°C (78.8°F), REM sleep was absent, but states of wakefulness and slow wave sleep were present and the same as those occurring at normal body temperatures. In each instance of torpor, sleep time increased, and the percent of time spent in REM sleep progressively decreased as body temperature declined.

(more)

SQUIRRELS (CONT'D)

Despite the suppression of REM sleep during torpor, compensatory REM rebounds did not occur in the 24-hour period following the return to usual body temperatures. Decreased body temperature or torpor appears to be associated more closely with the sleep state rather than a pre-established circadian variation of body temperature which is independent of sleep.

Sleep patterns during shallow torpor in the desert ground squirrels were qualitatively and quantitatively identical to those of shallow hibernation in alpine ground squirrels. Also, changes in EKG,EMG, and EEG activity during bouts of shallow torpor were similar to those of shallow hibernation.

Usually the function of sleep is hypothesized to be the restoration of one or more physiological processes depleted during prior wakefulness. However, the slow wave sleep found during hibernation probably evolved as an adaptation for energy conservation that partially offsets the high costs of endothermy, or being a warm-blooded animal. The temperature regulation adjustments found while entering torpor are probably an extension of those initiated during slow wave sleep.

In conclusion, the regulated decrease of body temperature in warm-blooded animals found during slow wave sleep indicating reduced metabolism is one inherited instinct for both states of hibernation and estivation and a very valuable physiological process for conserving energy.

This study was supported by NIH's National Institute of General Medical Sciences and conducted by James M. Walker, Ann Garber, H.C. Heller, and Ralph J. Berger at Thimann Laboratories, University of California, Santa Cruz. The story appeared in the June 8, 1979 issue of *Science*.

###

NINCDS SCIENTIST FINDS FOOD DYE AFFECTS BRAIN

A scientist at NIH's National Institute of Neurological and Communicative Disorders and Stroke has found the first laboratory evidence that low concentrations of Red No. 3, a widely used artificial food dye, can affect the brain.

Dr. Ellen K. Silbergeld and Jeffrey A. Lafferman reported in the July 27, 1979 issue of *Science* magazine that experiments on rat brain tissue reveal that erythrosin B (Red No. 3), partially blocks uptake of dopamine in brain cells.

According to the authors, this blocking action is consistent with the theory that Red No. 3 can induce hyperactivity in susceptible children.

Dopamine is one of the natural substances brain cells use to "talk" to each other, and is known to have a profound effect on human moods and movement. According to the report, Red No. 3 is about one hundredth as potent as amphetamines, an inhibitor of dopamine uptake known to produce excitable behavior.

While artificial food additives have been suggested to contribute to hyperactivity, Dr. Silbergeld cautions that "conclusive evidence is lacking."

"This study is provocative," she says, "but it doesn't prove that dyes in our food can affect the brain."

###

IC ANNOUNCES FELLOWSHIPS FOR WEDEN, SWITZERLAND, FRANCE

The Fogarty International Center, National Institutes of Health, has been asked to announce that the Swedish Medical Research Council, the Swiss National Science Foundation and the French National Institute of Health and Medical Research (INSERM) will each make available in 1980 several research fellowships to qualified U.S. biomedical scientists. These fellowships will provide post-doctoral training in basic or clinical areas of medical research.

To be eligible candidates must be citizens of the U.S.A. and have been engaged in independent responsible research in one of the health sciences for at least two of the past four years. Applicants must also provide evidence of acceptance by a training institution and preceptor. Stipends range from $11,000 to $16,700 per year, depending upon the Fellow's age, qualifications and experience.

The deadline date for the receipt of completed applications for the INSERM program is October 1, 1979. The deadline date for the Swedish and Swiss programs is February 1, 1980.

Application materials may be obtained from Scholars and Fellowships Program Branch, Fogarty International Center, NIH, Bethesda, MD 20205. Applications will be reviewed for scientific merit at the FIC and will then be forwarded to Sweden, Switzerland and France as appropriate for final selection.

###

Editors of publications may request a glossy print
of the photographs that appear in this Portfolio

Ms. Maureen Napper
National Institutes of Health
Building 31, Room 2B-10
Bethesda, Maryland 20014

Ms. Maureen Napper:

Please send me one glossy print of the photograph from the list below:

1624 _____

1625 _____

1626 _____

Name: ______________________

Title: ______________________

Publication: ______________________

Address: ______________________

City, State, Zip: ______________________

Telephone: ______________________

NEWS&FEATURES FROM NIH

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE■Public Health Service■National Institutes of Health■Office of Information■Bethesda, Maryland

LIBRARY
OCT 11 1979
NATIONAL INSTITUTES OF HEALTH

See page 6

September 1979

RESEARCH ADVANCES:

Radiation-caused Cancer Most Likely Found In Breast....................1
Weight Loss Maintenance Associated with Behavioral Factors..........3
Michigan Scientists Report How Some Bacteria Can Resist Antibiotics......8
Cyclophosphamide Causes Remission of Blood Vessel Inflammation..11
Ovarian Hormones May Influence Heart Disease Rate for Women.....13
Israeli Yemenite Follow-up Study Finds High Diabetes Incidence..17
Diabetes-like Kidney Damage Linked to Other Diseases............23
Value of Estrogen Replacement Discussed at NIA Conference.......27

Thomas H. Flavin, Acting Editor
Joyce F. McCarthy, Special Assistant
NIH News Branch
Building 31, Room 2B-10
Bethesda, MD 20205
Phone: (301) 496-1206

RADIATION-CAUSED CANCER
MOST LIKELY FOUND IN BREAST

In women past puberty, the breast is the organ most sensitive to cancer caused by radiation. This finding is supported with remarkable consistency by studies of a number of different exposed populations. Charles Land, Ph.D., a radiation epidemiologist at the National Cancer Institute, reported these findings September 6 at the National Conference on Breast Cancer in New York.

The excess risk of breast cancer arising from radiation exposure is approximately proportional to the dose received, Dr. Land said. The degree of risk does not appear to change for a total dose received in small exposures over a period of time, compared with the same dose received in a single exposure. The risk also is unaffected by the kind of radiation--X-rays or neutrons, for example. These findings imply that one can estimate with some confidence the risk associated with low-dose exposures to ionizing radiation, even though such estimates must depend heavily on data obtained at higher doses, Dr. Land said.

The studies have shown that excess risk depends heavily on a woman's age at the time of exposure to radiation. However, the women studied have been primarily in their second to fourth decades of life, leaving uncertainties about risks from exposure before puberty and after menopause. Women studied include those exposed to atomic bomb radiation in Japan and those exposed medically in the treatment of postpartum mastitis or tuberculosis.

Sensitivity to radiation does not seem to be affected by the underlying normal prevalence of breast cancer within various population groups, Dr. Land said. Even populations usually at low risk for breast cancer, such as the Japanese, experience the same degree of risk from radiation exposure as do populations with higher normal levels of breast cancer.

(more)

CANCER (CONT'D)

The age at which a woman is exposed to radiation does not seem to affect the age at which she subsequently develops breast cancer. Exposed women simply have proportionally more cases of breast cancer at every age than do unexposed women. This indicates that there is a strong influence of factors other than radiation involved in radiation-induced breast cancer, Dr. Land concluded.

###

WEIGHT LOSS MAINTENANCE ASSOCIATED WITH BEHAVIORAL FACTORS

By Wendy K. Bowis, a senior at
Wellesley College, Massachusetts

Many women can breathe a sigh of relief after finally taking off unwanted pounds, but for most overweight women the battle doesn't end there. The difficulty of maintaining weight loss is one of the major problems confronted by women who are anxious to lose weight. Researchers at the Medical College of Wisconsin in Milwaukee recently conducted a study to establish whether certain factors associated with the cause of obesity may also determine whether a woman will be capable of maintaining her desirable weight. This study was supported in part by NIH's National Institute of Arthritis, Metabolism and Digestive Diseases, and reported in the July issue of *Preventive Medicine*. Vol. 8, No. 4.

The subjects participating in the two-year study included 175 severely obese women ranging, on admission, in height from 58 to 72 in. and in weight from 174 to 500 pounds. Most of the women were in their 30s and 40s, although ages ranged from teens to 60s.

The format of the study required that the women spend three weeks in a Milwaukee hospital while they participated in a weight reduction program and comprehensive study of factors associated with obesity. They would then be followed for 18 to 24 months after discharge to observe their ability to maintain the achieved loss.

During the first week of hospitalization, each subject was put on a weight maintenance diet and given a complete physical examination. During this period the women completed two psychological tests--the Minnesota Multiphasic Personality Inventor (MMPI) and Michill Adjective Rating Scale (MARS)--as well as a questionnaire on possible obesity-causing factors such as weight history, medical history, eating habits, obesity of family members, and demographica.

(more)

WEIGHT LOSS (CONT'D)

The second and third weeks of the study involved a weight reducing 600 calorie diet, and counseling from the medical staff and dieticians about the medical risks of obesity and the necessity for appropriate exercise and food selection.

After leaving the hospital the women were encouraged to continue their membership in their local TOPS chapter (a weight reducing organization that partially sponsored the research study). This participation would insure the reporting of their monthly weight for the follow-up study. The local organizations also helped reinforce weight loss with weekly weigh-ins in front of club members, contests for the greatest weight loss, and diplomas for women who reached and maintained their physician's recommended weight goals.

At the end of the three-week hospital stay, the median weight loss was 15 pounds. At the end of the two-year follow up, 28 (16 percent) of the women had lost more than 40 pounds. 63 women (36 percent) had lost more than 20 pounds, 117 women (67 percent) had not regained the weight lost in the hospital, and 20 women (11 percent) were at least 20 pounds heavier than at admission to the hospital. Moreover, most women seemed to do better at maintaining weight loss for the first six to nine months after discharge than they did after nine months.

The weight change during the post hospitalization period was measured as the percentage weight change from discharge to time of last follow-up.

Various medical history characteristics of the women such as maximum and minimum weight as a teenager, weight or relatives, etc. were some of the factors correlated with the weight change following hospitalization. Eating habits, demographic factors, obesity history, and stress tolerance, were also factors studied in relation to weight change.

(more)

WEIGHT LOSS (CONT'D)

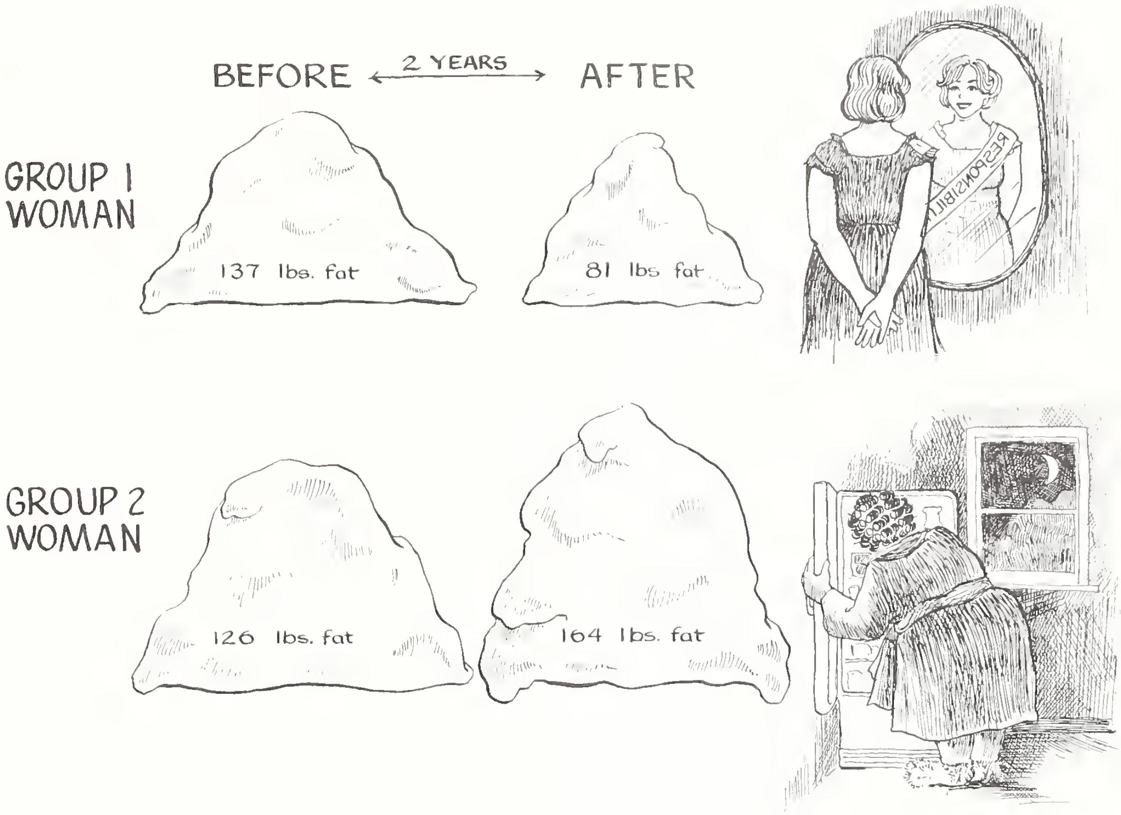
None of these items, however, were found to be associated with weight change. For instance a stress variable, a potential factor in obesity, such as the death of a child, did not indicate difficulty in maintaining weight loss. Fourteen women, who gained an average of 2.6 percent of their weight at discharge, responded that they had previously experienced the death of a child. Yet this differs only slightly from the 100 women who had never faced such a crisis and still experienced an average gain of 2.4 percent. In a similar example, women who reported having severe discomfort during menstruation gained no more weight after hospitalization than did the women reporting no discomfort. An average of 0.5 percent weight gain was calculated for both groups.

While eating habits such as snacking, rate, and time of good and poor appetite did not individually show significant correlations with weight change, a combination of the number of meals per day and time of strongest appetite might be associated with weight change. The results showed that women who had strong appetites in the afternoon or evening and ate no more than three meals a day had greater weight gains than did women whose appetites were also greater late in the day but who spread their food intake into four or more meals. It appears that a high concentration of total calories in the late afternoon or evening adversely affects the ability to lose weight.

The only other factors showing significant correlations with weight fluctuations and ability to maintain weight loss were the "responsibility" and "control" scales from the MMPI psychological test. Other variables on the test such as hypochondria, hysteria, dependency, and prejudice, all showed low correlation with weight change. The patients who indicated higher responsi-

(more)

WEIGHT LOSS (CONT'D)



Successful weight loss maintenance is represented by the Group 1 woman's enhanced self-awareness and responsible behavior. Unsuccessful weight loss is shown by the Group 2 woman's lack of self-awareness (control) and nocturnal eating habits. (NIH Photo #1627)

(more)

bility, had the greatest weight losses, while weight loss decreased for patients with higher scores for control.

Since "responsibility" suggests dependability, trustworthiness, and willingness to accept the consequences of one's own behavior, a responsible person in a weight control program may be more likely to cooperate with his physician and assume responsibility for his weight control. Thus, greater responsibility can be expected to correlate with better weight maintenance.

The researchers also offered an interpretation of the negative correlation between the "control" scale and maintaining weight loss. "Control" can be considered as the individual's tendency to deny that she has socially unacceptable behavior and impulses. Women with greater control seemed less self-aware of their own impulses and did not acknowledge that their behavior with regard to diet was unacceptable.

In summary, only three factors were found to be associated with the ability to maintain weight loss following an intensive weight reduction program: the Control and Responsibility scales of the MMPI and a combination of number of meals per day and time of strongest appetite. Since no common etiologic factors in obesity were important in determining the success of weight loss and weight maintenance, weight loss must, therefore, be dependent on the ability to modify some behavior affecting obesity. Further studies should be focused on what factors changed in the women's ability to lose weight, such as eating habits on activity level, as well as what factors, such as motivation for losing weight or spouse support, would enable the subjects to make these changes.

The investigators conducting this research were Arthur J. Hartz, Ph.D., Ronald K. Kalkhoff,M.D., Alfred A. Rimm, Ph.D., and Raymond J. McCall, Ph.D.

###

MICHIGAN SCIENTISTS REPORT HOW SOME BACTERIA CAN RESIST ANTIBIOTICS

Investigators at the NIDR-supported Dental Research Institute of the University of Michigan in Ann Arbor, have reported a new way that some bacteria acquire resistance to antibiotics.

Certain strains of *Streptococcus faecalis*, a common cause of root canal infections, produce a substance analagous to sex pheromones in animals. This substance causes other strains of the bacterium to become adhesive and cluster together. The formation of concentrated masses of sticky bacteria aids the process of conjugation (mating).

In conjugation, two cells representing different strains form a temporary close contact, and some genetic material passes from one of the cells (the donor) to the other (the recipient). However, donors generally do not conjugate with donors nor recipients with recipients. Thus, in addition to ordinary vegetative reproduction by cell division, some bacteria have this rudimentary type of sexual reproduction. Conjugation can result in the rapid spread of genetic traits such as drug resistance in bacterial populations.

Resistance to antibiotics and production of hemolysin (ability to destroy red blood cells) are traits frequently carried on small circular bits of DNA called plasmids rather than on the large, single, bacterial chromosome. Considerable research by other microbiologists, also supported by NIH, shows that various bacterial inhabitants of the mouth and of the intestine have developed a variety of ways of sharing plasmids. Many plasmids are self transferable, promoting conjugation; and bacteria that harbor these plasmids are, by definition, donors.

However, in *Streptococcus faecalis* the method of cell-to-cell passage of

(more)

genetic material has certain unique features. This organism is not motile, yet cells do join. It appears to lack slender, thread-like, pili that help some bacteria to attach to each other. Moreover, other processes for transferring plasmids (transduction and transformation) are unknown in this species. Nevertheless, Don B. Clewell and co-workers at the Dental Research Institute, as well as other investigators, have observed that several plasmids found in individual *Streptococcus faecalis* cells readily spread to cells that had no plasmids. In addition, these plasmids seemed to increase the spread of other genetic traits. Some scientists have even reported that plasmids have promoted conjugation between *Streptococcus faecalis* and other streptococcal species.

Searching for the explanation of how plasmids spread in this species, the microbiologists found a clumping agent. They observed that when donor or recipient strains are cultured separately, the cells disperse evenly through the liquid medium; but in cultures that combine both strains, large clumps or aggregations form.

When the scientists remove the cells from pure cultures of recipients and add samples of the remaining medium to pure cultures of the donor strain, clumping soon occurs; but when similar cell-free samples of donor's medium are added to a pure recipient strain, the cells continue to be dispersed. Clearly the recipient bacteria release a substance that causes donor cells to stick together and to other nearby cells.

This chemical, which Dr. Clewell calls CIA (clumping-inducing agent), is a small, heat-resistant molecule that can be inactivated by trypsin. At least 30 minutes must pass before donor bacteria exposed to it will clump. This

(more)

reaction does not require synthesis of DNA but does depend on synthesis of RNA and new proteins. Thus CIA acts as a signal or sex pheromone for the opposite (donor) strain of bacteria.

Production of CIA is not uniform in *Streptococcus faecalis*. Some recipient strains without plasmids make more CIA than others; and some bacteria with plasmids also make CIA. One plasmid that conveys resistance to tetracycline has no discernible effect on the response of donor organisms to CIA nor on the ability of recipient bacteria to make CIA, whereas other plasmids influence both of these phenomena. Dr. Clewell's research team identifies many of the plasmids they study by their ability to destroy red blood cells, but a number of them also convey resistance to antibiotics.

The scientists note that when recipient bacteria have received certain transferable plasmids, they usually cease to make CIA, become donors and, in turn, are aggregated by the CIA of other recipients. This sex-shuttling process also hastens the dissemination of antibiotic resistance and of other traits.

Gary M. Duny, Byron L. Brown, and Don B. Clewell reported their research last year in the *Proceedings of the National Academy of Sciences*. Further information was given at the March 1979 annual meeting in New Orleans, LA, of the International Association for Dental Research by Y. Yagi and D. B.Clewell (Abstract #979).

###

CYCLOPHOSPHAMIDE CAUSES REMISSION OF BLOOD VESSEL INFLAMMATION

Scientists of the National Institute of Allergy and Infectious Diseases (NIAID) have reported dramatic results in the treatment of severe systemic necrotizing vasculitis by use of the cytotoxic drug cyclophosphamide in patients unresponsive to steroids alone. Complete remission was achieved in all of the 17 patients with this highly lethal form of vasculitis who were studied at the National Institutes of Health Clinical Center over the past 11 years. No relapses were observed during cyclophosphamide therapy, and the supplementary dosages of steroids could be reduced or eliminated.

The vasculitis syndrome is characterized by inflammation of the blood vessel wall and damage (necrosis) of the tissues within or surrounding the vessel. Any size or type of blood vessel may be affected, and serious illness results when vasculitis afflicts the vessels serving vital organs such as the kidneys. Vessel damage is believed to be caused by the misdirected activity of the body's immune system. In this regard, cyclophosphamide suppresses the overactive immune system.

Serious vasculitis, although uncommon, usually presents in a variety of clinical forms. Severe systemic necrotizing vasculitis is a particularly serious form of vasculitis which involves the blood vessels of vital organs and often leads to irreversible impairment of the function of these organs. If left untreated, the five-year survival rate is about 15 percent. Treatment with steroids improves the five-year survival to 43 percent but does not always halt the ultimate progression of the disease.

All patients in the NIH study had severe disease with involvemnet of multiple organs. In several patients, extremely high doses of steroids had

(more)

produced incapacitating side effects but failed to control the vasculitis.

Initially, all patients in the study were treated with a standard dose of cyclophosphamide (2 milligrams of drug per kilogram of body weight per day). After remission was achieved, lower maintenance doses were adjusted to individual patient requirements. In most cases, remission was evident within two to three weeks of the start of cyclophosphamide therapy. The average remission time was 22 months, although the range was 2 to 61 months.

Remission was defined as (1) the reversal of vessel or organ impairment caused by previously uncontrolled vasculitis or (2) the cessation of further organ involvement, especially in advanced cases, after the initiation of cyclophosphamide treatment. Most remissions were of the first type.

The large variation in remission time was not related to patient responsiveness. Instead, it was tied to the fact that individual patients entered the study at different points within the 11-year period and had subsequent differences in length of follow-up time.

Three patients died during the study, two of causes unrelated to vasculitis. All three were in remission. Only one died of the late complications of his original disease, which had reached advanced stages before his entry into the study.

This work was conducted by Drs. Anthony S. Fauci, Paul Katz, Barton F. Haynes, and Sheldon M. Wolff at the NIAID's Laboratory of Clinical Investigation. Dr. Wolff is now at Tufts University. The four investigators reported their findings in the August 2, 1979 edition of the *New England Journal of Medicine*.

###

OVARIAN HORMONES MAY INFLUENCE HEART DISEASE RATE FOR WOMEN

By Ann L. Rinebolt
Summer Information Intern

Ovarian secretion of sexual steroid hormones may be responsible for the low incidence of heart disease found in pre-menopausal women. The results of this study on the effect of the menstrual cycle and lipid and metabolism suggest a causal relationship between hormones and atherogenesis, a forerunner of heart disease.

The study was conducted by Drs. Hak-Joong Kim and Ronald K. Kalkhoff at the GCRC Medical College of Wisconsin and was supported by NIH's Division of Research Resources. The article appeared in the June 1979 issue of *Metabolism*.

The low rate of cardiovascular disease in women has long been noticed, with the lowest incidence of one in 10 occuring premenopausally, as compared to an incidence of one in three in men.

Fourteen healthy women with regular menstrual cycles and 10 healthy men, all within 10 percent of their ideal body weight (as defined by the Metropolitan Life Insurance tables) were studied. The days within each woman's cycle were divided into four different phases: menstrual, follicular, ovulatory and luteal. For experimental purposes, each man was assigned an arbitrary four-week cycle, which was then broken down into four phases.

Each subject had a blood sample taken every 3-5 days after an overnight 14-hour fast. The women were sampled through three complete cycles and the men for two complete months.

Plasma was collected from the blood samples immediately, and then stored at 4° C until fractionated into very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL). Lipoproteins are a combination of lipids and proteins found in the blood which possess the general

(more)

HORMONES (CONT'D)

properties of proteins. B-lipoproteins transport most of the total blood plasma cholesterol.

These and the total plasma triglyceride (TG) and Chol (cholesterol) concentrations were measured and further broken down to isolate the cholesterol content of each of the lipoproteins: VLDL-Chol, LDL-Chol, and HDL-Chol.

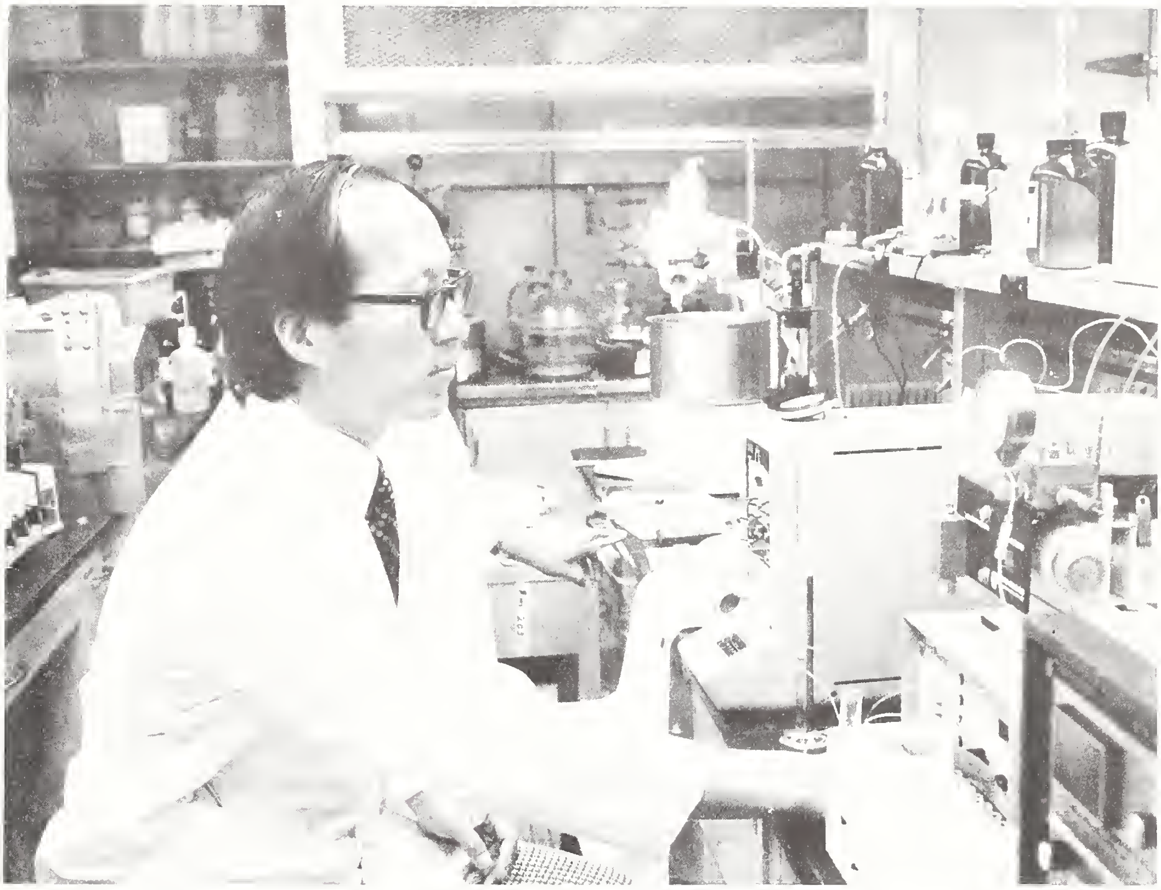
At any time interval, the peak TG (triglyceride) levels in women were found to be considerably higher than the mean levels found in men. LDL-Chol values in women were found to be significantly low in the luteal phase (medically termed "yellow body", meaning a yellow glandular mass (corpus luteum) in the ovary formed by the ovarian follicle that has matured and discharged its ovum. If not impregnated, the corpus luteum degenerates and shrinks; it secretes the hormone progesterone). In all other phases, LDL-Chol values were far below all mean values recorded for males. HDL-Chol rose slightly in women during the luteal phase, and was higher than men at all times during the cycle.

The lower LDL-Chol level in women corresponds to the pattern of sexual difference that has found a greater rate of atherosclerosis in persons with higher levels of LDL-Chol. Other recent studies have suggested that apoB, the principle carrier protein of cholesterol in LDL, primarily functions in transporting cholesterol to peripheral tissues. Therefore, levels of LDL and total body cholesterol pool size are linked.

Conversely, HDL-Chol levels are highest when total cholesterol pool size is low. It's carrier protein, apo-AL, is thought to expedite removal of cholesterol from tissues, therefore making it the protective mechanism against the high cholesterol levels found in women.

(more)

HORMONES (CONT'D)



Dr. Hak-Joong Kim of the Medical College of Wisconsin conducting research supported in part by NIH's Division of Research Resources on ovarian steroid hormones and lipoprotein levels. (NIH Photo #1628)

(more)

HORMONES (CONT'D)

Research in diabetes also supports the linkage theory between lipoproteins and heart disease. Dr. Allan L. Kennedy and his team of researchers at Royal Victoria Hospital in Belfast, Northern Ireland, have found a much higher level of HDL-Chol in adult onset diabetes, suggesting a reason for the greater incidence of atherosclerosis found in adult onset diabetes than in juvenile onset diabetes.

The relationship of the lipoproteins LDL-Chol and HDL-Chol to the menstrual cycle itself is observed in the luteal phase. Prior to the luteal phase, the level of estradiol (an estrogenic steroid hormone) is at its peak because ovulation had just occurred. As previously noted, it is during the luteal phase that the LDL-Chol and HDL-Chol levels reach their respective low and high peaks in women. This relationship suggests that estrogenic hormones somehow exert a suppressant effect on female cholesterol levels.

A possible explanation for the delay in cholesterol level drop found during passage from ovulation to the luteal phase may be the half life of LDL-apoB. The carrier protein has a relatively long plasma half life of four days, which is long enough to keep the cholesterol levels from changing before the beginning of the luteal phase.

This theory that estrogen has a suppressant effect on cholesterol levels has been supported by previous studies conducted on middle-aged or elderly men and ovarrectomized or postmenopausal women who have been found to have a higher susceptibility to heart disease perhaps because of the absence of estrogenic hormones.

###

NEWS & FEATURES From NIH September 1979

ISRAELI YEMENITE FOLLOW-UP STUDY FINDS HIGH DIABETES INCIDENCE

By Joyce F. McCarthy

In a population in which almost no diabetes was detected 20 years ago, new immigrant Yemenities in Israel now have an incidence of diabetes comparable to other affluent communities.

A different environment combined with metabolic changes caused by obesity seem to be causative factors for an 11.8 percent increase of diabetes in this unique population. It has also been found that the mortality rate from coronary artery disease in new immigrant Yemenites was low in the first decade after settlement but increased in the following decade.

Born in Yemen, a country situated in the southeast corner of the Arabian Peninsula and bordered by Saudi Arabia and the South Arabian Republic, the Yemenites immigrated to Israel 25 years ago and settled into six agricultural communities. In one year, from June 1949 - June 1950, about 43,000 Yemenite Jews were flown en masse to Israel through an arrangement called "Operation Magic Carpet." About 2,000 Jews emigrated after this date, and in 1968 there were about 200 Jews left in Yemen.

The Yemenites came from a backward and underdeveloped country whose economic structure and development was on a par with the Middle Ages. The changes which the Yemenite Jews underwent in Israel were not restricted to the economic and social spheres but were also of a cultural nature. The world of the Jew in the primitive and patriarchal way of life in Yemen was complete and stable, undisturbed by upheavals.

As a result of their confinement and isolation in the Arabian Peninsula and exclusion from non-Jewish culture, they had preserved the Jewish way of life of ancient times. This applied to their speech and pronunciation, dress,

(more)

art, music, and dances. Jewish social life was based on the foundation of religious culture; daily prayers in the synagogues accompanied by the study of the Torah.

In Israel the Jews of Yemen were suddenly uprooted from a peaceful medieval form of life and thrust into modern 20th century Western life. At the end of 1965 the estimated Yemenite population of Israel was 150,000. At the time of immigration, the majority of Yemenites both urban and rural were earning their living from manual labor. Since then, veteran members of the community have risen in social scale and their characteristic leanness has gradually disappeared with the improvement of nutritional standards, although the adoption of the Israel diet has made them susceptible to certain illnesses from which they were previously virtually immune.

Of 306 Yemenites studied (182 males and 124 females aged 30 years and over), diabetes incidence rose 13.2 percent in males and 9.7 percent in females. The male/female ratio was affected by weight status -- diabetes was more prevalent in underweight males and in overweight females; the rate of diabetes in underweight females equaled that of the males. In this population, obesity resulted in an increase in the precent of diabetes in all female age groups, whereas in males, obesity resulted in an increase of diabetes in the 55 years and older age group only. These results are in accordance with the fact that obesity significantly alters glucose tolerance.

Medical histories were obtained and physical exams were given to each patient. Those patients with diabetes or vascular disease were not included in the study. Patients fasted overnight and venous blood was then collected

(more)

YEMENITES (CONT'D)

The culture of the Yemenite community was more outstanding for its Jewish tradition than that of any other Jewish community. Goldsmithery and embroidery were the most prominent crafts that the Yemenites brought to Israel. (NIH Photo #1629)

in heparin (an anticoagulant) to determine glucose levels, and plasma lipids and lipoproteins were analyzed. Subjects were then divided into underweight and overweight groups.

The patients received 1 gram of glucose per kilogram of body weight and blood samples were analyzed 30, 60, and 120 minutes after administration to determine glucose and insulin response. These results were statistically evaluated and graphic curves were plotted to show the time of the maximal peak response.

The insulin response curve results showed 39 percent of the underweight nondiabetics had a maximum insulin response at 30 minutes. Only 8.3 percent of the underweight diabetics peaked at 30 minutes. At 60 minutes, 48.4 percent of the nondiabetics and 50 percent of the diabetics had a peak. In the overweight category, 28 percent of the nondiabetic subjects and 8.3 percent of the diabetics had a maximum response curve at 30 minutes whereas 48 percent of the nondiabetics and 50 percent of the diabetics had a delayed response with a peak at 60 minutes.

In this study, it is apparent that in maturity-onset diabetes, 91.7 percent of the underweight and 91.7 percent of the overweight had delayed insulin response. Significantly, among the nondiabetics, 53.4 percent of the underweight and 68 percent of the overweight also had delayed insulin responses with peaks at 60 and 120 minutes following glucose administration.

The insulin response curve differences between diabetics and nondiabetics were not significant except in those cases with the 30 minute maximal response. In the underweight group, the fasting insulin levels between maturity-onset

(more)

diabetics and nondiabetics were not significant. In the overweight group, the fasting insulin level of diabetics was higher than the respective nondiabetic groups.

This result is attributable to hyperglycemia (too much blood sugar), since insulin increments at these times equaled those present in normal glucose tolerance, both in the underweight and overweight subjects. It appears that in order to explain this fact, it is necessary to apply the theory of "insulin resistance" or suggest that the insulin molecule itself is structurally not intact. Obesity is frequently cited as a cause of insulin ineffectiveness, but this ineffectiveness was also evident in the nonobese diabetic subjects.

Adult-onset diabetes is often defined as undue hyperglycemia resulting from an inadequancy of insulin. However, these results suggest that there is a deficiency of insulin action rather than a shortage of insulin.

Analysis of plasma cholesterol and LDL (low density lipoproteins)-cholesterol levels were found to be significantly lower in the nondiabetic Yemenite settler described here compared to the non-Yemenites. Plasma triglycerides (TG) were increased in the diabetics, both male and female. The LDL-Cholesterol levels were increased in males while no consistent trend was noted in the HDL (high density lipoproteins)-cholesterol levels. In the underweight man or woman, HDL/LDL ratio is not affected by diabetes, but in the overweight male or female, diabetes results in a decreased HDL/LDL ratio.

In this unique Yemenite population in Israel, the incidence of hyperlipoproteinemia among the diabetics was more than twice that of nondiabetics, 27.7 percent and 11.0 percent respectively. The percent of the subjects with

(more)

YEMENITES (CONT'D)

different types of hyperlipoproteinemia was similar to that reported by other investigators.

These observations indicate that the increase of plasma lipid levels occuring in the Yemenite population during the 25 years following immigration to Israel, were most probably due to changing environmental conditions. In addition, the expression of diabetes in this population in relation to plasma lipid and lipoprotein levels were found to be similar to that of other non-Yemenite diabetic populations.

This research was conducted by Drs. A.M. Cohen, J. Fidel, B. Cohen, A. Furst, and S. Eisenberg from the Diabetic Unit and the Isotope Laboratory for Endocrine Research and the Shimshon Family Medical Center, Kupat Holim Beit-Shemesh, Departments of Internal Medicine A and B, Hadassah University Hospital and Hebrew University, Hadassah Medical School, Jerusalem, Israel. The study was supported in part by a grant from NIH's National Institute of Arthritis, Metabolism, and Digestive Diseases and appeared in the July 1979 issue of *Metabolism*.

###

NEWS & FEATURES From NIH September 1979

DIABETES-LIKE KIDNEY DAMAGE LINKED TO OTHER DISEASES

By Dinah M. Bertran

In what sounds like a medical detective story, serious diabetic-like changes have occasionally been found in the kidneys of patients who have never had hyperglycemia, or elevated blood glucose, the metabolic abnormality most characteristic of diabetes mellitis. Recently, researchers have carefully studied two patients who had no history of hyperglycemia but who previously were diagnosed as having diabetic glomerulosclerosis. Through closer scrutiny, however, they were found to have had other diseases.

These two cases were reported in the June 1979 issue of *The American Journal of Medicine*. The researchers point out that these two cases (from 477 cases examined) reflect the incidence of rare occurrences reported in literature concerning non-hyperglycemic patients diagnosed as having diabetic glomerulosclerosis. The investigators suggest that any patient with normal plasma glucose levels who appears to have diabetic glomerulosclerosis be carefully reexamined for a possible prior history of diabetes. If no incidence is found, the patients should be further examined for other possible causes of the kidney lesion.

Diabetic glomerulosclerosis eventually leads to kidney failure. In diabetics of long standing, despite the current regimen of clinical control, degeneration of the capillaries occurs. Diabetic glomerulosclerosis (d.g.) is a particular type of degenerative disease that occurs only in the kidneys of diabetes mellitus patients. D.g. involves a hardening of the glomeruli (clusters of blood vessels) in the kidneys. Diagnosis is achieved by examining tissue from renal (kidney) biopsy. There are certain morphologic (tissue structure) characteristics of d.g. which make differentiation between that and some other illnesses hard to distinguish.

(more)

KIDNEY DAMAGE (CONT'D)

The investigators reviewed their work, spanning a period of four years, of 477 renal biopsies. Of these, they found 25 that had been diagnosed as d.g. They evaluated the clinical history of these 25 patients to find the non-diabetics, and found two who had no current or prior history of elevated blood glucose. The biopsies from these two patients were then further reexamined. In both cases, the diagnosis was subsequently revised, uncovering diseases other than diabetes which they believed were responsible for the kidney lesions.

In one of the two cases, the negative history of hyperglycemia led the investigators to suspect light chain nephropathy (an inflammation of kidney glomeruli due to an illness called light chain disease). Reexamining the biopsy specimens using anti-light chain reagents, the investigators revised their initial diagnosis from d.g. to light chain disease.

Light chain disease is usually due to malignancy (cancer) of the plasma cells. These are the cells in the body in which antibodies, the proteins which fight disease, are produced; light chains are a part of the antibody molecules.

The more detailed histologic study of the kidney of this particular patient revealed that the kidney lesion was not the result of diabetes, but rather light chain disease caused by a form of cancer.

In the second of the two cases, the patient again had no history of hyperglycemia. His renal biopsy was originally diagnosed as d.g. During two and a half years of follow-up therapy, his serum glucose determinations were repeatedly normal (no clinical signs of diabetes). A repeat renal biopsy was performed by the investigators, resulting in a revised diagnosis of lobular or membranoproliferative glomerulonephritis. This is an illness similar to d.g.,

(more)

KIDNEY DAMAGE (CONT'D)

in that the glomeruli of the kidneys are seriously afflicted. Specifically, the capillary loops in the glomeruli become inflamed. It occurs in acute or chronic forms, but rather than being caused by diabetes, it is usually a secondary effect of an infection, particularly by streptococcus bacteria. Glomerulonephritis has also been reported in connection with allergic reactions to poison oak.

In their article, the researchers state that diagnosis of diabetes can be hard to determine. They make two points; 1) in a patient diagnosed as non-diabetic, yet seen to have d.g., it must be ascertained that he was not and never had had hyperglycemia. They mention that obese patients can have hyperglycemia which becomes normalized after weight loss and adhering to a low-calorie diet. The patients could actually have d.g. as a result of previous hyperglycemia, although at the time of renal biopsy their blood glucose levels were normal; and 2) in those patients who have never had elevated blood glucose, but who are diagnosed as having d.g., another illness must be thoroughly checked for. It should be noted that since at present there is no genetic marker for diabetes which establishes the presence or absence of the disease with certainty, it remains possible that a patient may have d.g. without hyperglycemia as an independent manifestation of the underlying diabetic condition.

In addition to the two diseases previously mentioned, a third disease that can mimic the pathologic signs of d.g. is amyloidosis. Amyloidosis is the accumulation of a complex protein in the tissues which vaguely resembles starch. It is sometimes associated with cancer of the bone marrow. Careful histologic examination will generally permit the distinctions to be made between d.g.

(more)

and amyloidosis.

The serious nature of these alternative diseases points to the importance of careful diagnosis of diabetic glomerulosclerosis in any person without a history of hyperglycemia. The authors warn against considering an individual to be just an occasional patient with a diabetes-caused disorder who unaccountably never had diabetes.

The risk of this misdiagnosis is evident, especially when the patient examined with closer scrutiny may have a potentially treatable illness such as a secondary strep infection or even a form of cancer.

This research was conducted by Drs. Steven Herf, Stephen L. Pohl, Benjamin Sturgill, and Warren K. Bolton, from the Diabetes Research Center and the Department of Medicine and Pathology, University of Virginia School of Medicine, Charlottesville, Virginia. This study was supported in part by grants from NIH's National Institute of Arthritis, Metabolism and Digestive Diseases.

###

NEWS & FEATURES From NIH

September 1979

VALUE OF ESTROGEN REPLACEMENT DISCUSSED AT NIA CONFERENCE

To be or not to be an estrogen user--that is the question millions of women who are undergoing or are past menopause (about age 50 or over) are asking their physicians and themselves. This question was the topic of an NIH Consensus Development Conference on Estrogen Use and Postmenopausal Women, sponsored by the National Institute on Aging, held September 13-14, 1979.

Drugs containing the female sex hormone estrogen are known to alleviate hot flashes and vaginal changes such as decreased lubrication and elasticity that can make urination and intercourse painful for postmenopausal women.

Estrogen is also thought to help prevent or arrest osteoporosis, a brittleness of bone that leads to hip fractures and other debilitating injuries in many elderly women.

Other evidence suggests, however, that estrogen use may increase the risk of developing cancer of the lining of the uterus, known as endometrial cancer. Although there is no convincing evidence, there is some concern that estrogen use may increase the likelihood of developing breast cancer and cardiovascular conditions such as high blood pressure and heart attack.

The September 13-14 conference on the estrogen dilemma is part of a series of consensus development conferences organized by the National Institutes of Health's Office for Medical Applications of Research. These conferences represent an NIH effort to communicate the latest research findings to practicing physicians and the public and to reach agreement, wherever possible, on the effectiveness and safety of various diagnostic and treatment approaches.

The estrogen issue is particularly difficult because so many women are exposed to this substance their entire adult lives--first for birth control and

(more)

later for menopausal symptoms.

The Consensus Conference brought together researchers, gynecologists and other physicians in clinical practice, consumer groups, women's organizations and members of the public in an effort to reach general agreement on the benefits and risks of estrogen therapy in managing menopausal and postmenopausal conditions.

Several speakers presented papers on various aspects of postmenopausal estrogen therapy, including its benefits in treating menopausal symptoms and preventing osteoporosis, and its relative risks.

Members of the audience and a Consensus Development Panel of about a dozen health professionals and concerned individuals responded to these presentations.

For more information about results from this conference please contact Maureen Mylander at The National Institute on Aging, Building 31, Room 5C-36, Bethesda, Md. 20205, or at (301) 496-1752.

###

Editors of publications may request a glossy print of the photographs that appear in this Portfolio

---

Ms. Maureen Napper
National Institutes of Health
Building 31, Room 2B-10
Bethesda, Maryland 20014

Ms. Maureen Napper:

Please send me one glossy print of the photograph from the list below:

1627 _____

1628 _____

1629 _____

Name: ____________________

Title: ____________________

Publication: ____________________

Address: ____________________

City, State, Zip: ____________________

Telephone: ____________________

NEWS&FEATURES FROM NIH

PORTFOLIO — NIEHS

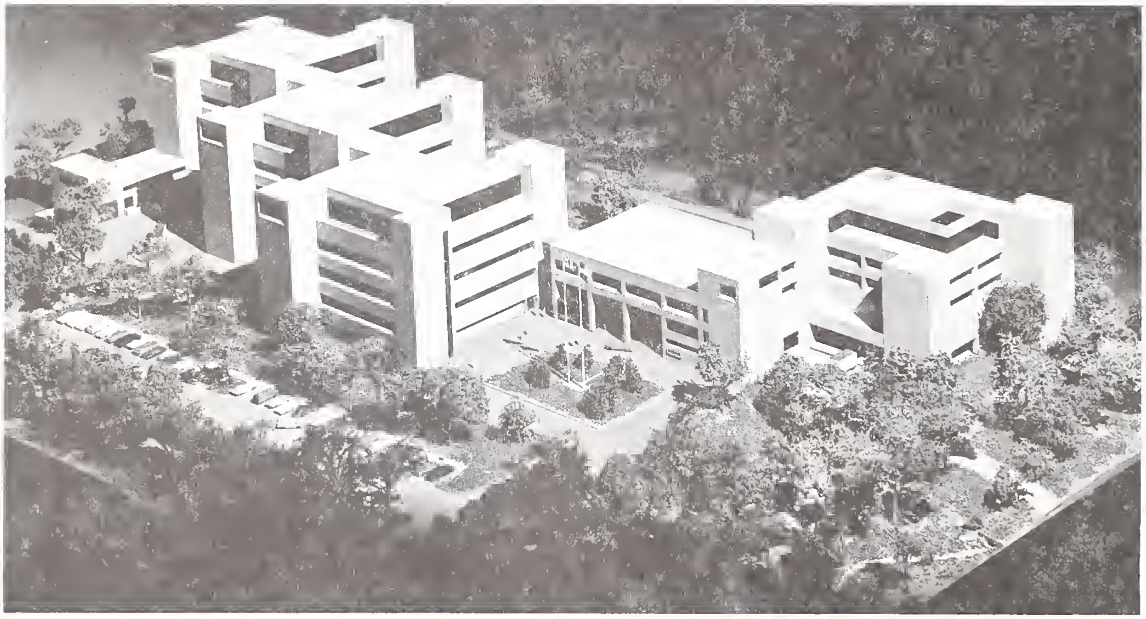
U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE ■ Public Health Service ■ National Institutes of Health ■ Office of Information ■ Bethesda, Maryland 20205

LIBRARY
NOV 27 [illegible]
NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

NOVEMBER 1979

Thomas H. Flavin, Acting Editor
Joyce F. McCarthy, Special Assistant
NIH News Branch
Building 31, Room 2B-10
Bethesda, MD 20205
Phone: (301) 496-1206



This NIEHS South Campus structure, now under construction in Research Triangle Park, N.C., will have a total gross area of 334,000 sq.ft. It will be composed of five interconnected units or modules housing laboratory and animal science facilities, support functions and general administration services. The modules are laid out in a staggering pattern to minimize environmental impact and to maximize the view of the 29-acre man-made lake and natural surroundings. Portions of this center are now occupied with a phased-in occupancy of the five-module building scheduled to begin in 1981.(NIH Photo #NP-1)

Dr. David P. Rall has been Director of the National Institute of Environmental Health Sciences since 1971. Among his many areas of expertise, he has extensive experience in comparative pharmacology, cancer chemotherapy, pesticide toxicology, and drug research and regulation. He is also chairman and coordinator of various exchange programs in environmental health between the U.S. and the U.S.S.R. Dr. Rall also serves as the Director of the National Toxicology Program. This program was initiated in 1978 to strengthen DHEW's activities in the testing of chemicals of public health concern as well as in the development and validation of new and better integrated test methods. (NIH Photo #NP-2)

PORTFOLIO ON THE NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

INTRODUCTION

Every year approximately 2,000 new chemical compounds enter our environment in significant commercial quantities. These new chemicals join some 15,000 synthetic chemicals currently present. Many of these compounds are harmless while others could be causative agents in the development of major chronic diseases of the heart, lungs, nervous system, as well as certain cancers, and structural and functional birth defects.

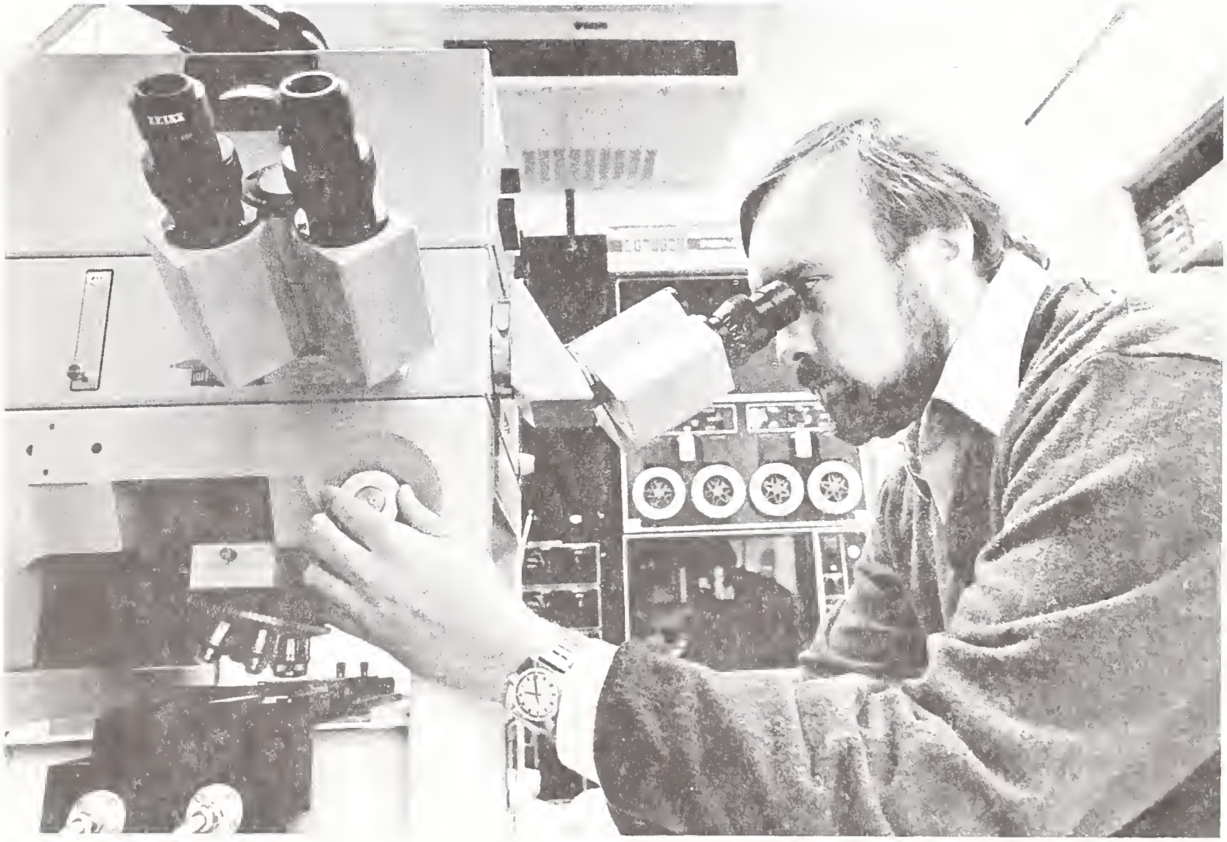
Many researchers believe that 90 percent of all human cancer is of environmental origin; other contributing factors have been identified as being genetic, viral, or from radiation. In addition, the toxic effects of environmental pollutants within our environment can cause kidney, liver, neurologic and genetic disorders, and act adversely on the immunologic and reproductive systems.

In 1969, the National Institute of Environmental Health Sciences (NIEHS) became the 10th Institute within the National Institutes of Health. NIEHS investigates and funds basic and applied research on the health effects of exposure of man and other biological systems to potentially toxic or harmful chemical, physical, and biological environmental agents. Its goal is to provide the scientific information base, advanced methodology, and trained manpower to understand the impact of these environmental factors on human health and well being.

Once this information base is developed, it is transmitted to the regulatory agencies, other Government agencies, legislators, the medical and research communities, industry, and the general public.

NIEHS research is conducted in part at its own laboratories in Research Triangle Park, North Carolina. The Institute also supports research and training through grants and awards at colleges, universities, and non-profit laboratories throughout the country. In addition, NIEHS has satellite marine biomedicine laboratories at the CV Whitney Marine Laboratory in Florida, and a seasonal laboratory at Mt. Desert Island in Maine, for studying the effects of pollutants on marine species.

NIEHS supports and conducts research on: how and where potentially harmful environmental agents are released into the environment; how these agents move, and possibly change as they move; the extent of exposure of various population groups, especially those groups sensitive to these agents; what effects these agents cause by themselves and in combination with other agents in the environment; what happens in biological systems after exposure to hazardous agents; and what diseases, disabilities, or developmental deficits, are caused or aggravated by these agents.

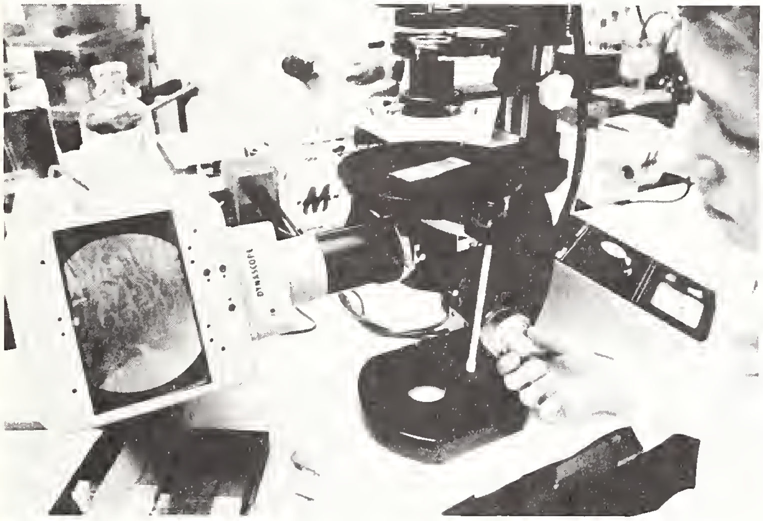


(NIH Photo #NP-3)

Toxicity Testing Systems

The Institute supports efforts to identify hazardous environmental agents before they are released into the environment. This work includes development, testing, and validation systems to predict the toxicity in man occuring from exposure to environmental factors.

The development of simple, rapid prescreens and toxicity tests, with emphasis on those which identify environmental agents causing genetic damage (mutagenicity), birth defects (teratogenicity), target organ damage, and reproduction system anomalies, are of special interest to NIEHS scientists. Research emphasis is placed on determining the validity of the testing procedures, and projecting results from laboratory animal studies to man.



Dr. Carol Schiller uses a light microscope in the Laboratory of Organ Function and Toxicology at the National Institute of Environmental Health Sciences in Research Triangle Park, N.C. NIEHS is the principal Federal agency for research on the health effects of environmental agents. (NIH Photo #NP-4)

Mutagenesis

Recent studies on chemical compounds which were once considered safe for human use have shown chromosomal and genetic damage. NIEHS scientists, therefore, are conducting mutagenicity testing using experimental organisms that range from microbes to mammals. The development of new mammalian test systems, including human cells in tissue culture, and the extrapolation from these experimental test systems to man are being pursued in an effort to unravel the complex issues of environmental health research.

To address the issues, the Institute is developing a three-level mutagenesis testing program that could test up to 1,000 chemicals yearly in microbial systems ranging from bacteria, *in vitro* mammalian cell systems, insect systems, and continuing up to whole animal models. Chemicals showing mutagenicity in these systems will be further tested using long term bioassays. By using these methods, the Institute hopes to develop and validate the most accurate and efficient tests for determining the health effects of toxic substances in the environment.

Teratogenesis Test Systems and Reproduction Toxicology

This research area studies the effect of environmental agents on reproduction and development. Focus is on the developmental effects of offspring exposed pre-or postnatally to drugs and common chemicals through their mothers. Institute scientists have developed models to study the mechanisms of such effects and are seeking reliable animal models that will forecast damage in humans.

Recent studies have been conducted on the effects of DES (diethylstilbestrol), a synthetic estrogen hormone. DES has been controversial because of its carcinogenic potential for women exposed prenatally. It was given to mothers of these women in hope of preventing miscarriage. Studies on mice have shown that prenatal exposure to DES adversely affects the reproductive capacity of female mouse offspring; this effect is dose-related, and the female loses the ability to ovulate. The reproductive capability of male mouse offspring is also affected, with 60 percent found sterile after prenatal exposure. These results are pertinent to the development of an animal model for study of reproductive tract lesions in humans whose mothers were given DES during pregnancy.

NIEHS scientists are currently studying blastocysts, perinatal ovarian tissues, embryos in culture, as well as the more routine cell lines for teratogenesis testing. A reproducible *in vitro* system for culturing postimplantation rat and mouse embryos has also been established. Embryos are maintained in culture (24-28 hours), consistent with normal *in vivo* development, and are constantly monitored during critical periods. The merit of this culture system for predicting teratogenicity is being compared to slower studies involving whole animal models. The culture system also provides for a more in-depth model of molecular events which constitute normal development.

Because of the amount of new scientific literature, the NIEHS has developed the Environmental Teratology Information Center (ETIC). The ETIC data base contains information that has been gathered from the open literature that reports on the testing and evaluation for potential teratogenesis of environmental chemical and biological factors and physical agents. The Center's file currently has over 15,000 entries which contain bibliographic details, keywording of chemicals, systems studied, and test organisms. The agent index contains over 6,000 individual agents. Over 5,000 of these are chemicals of which approximately 4,500 have been cross indexed with the CAS (Chemical Abstract Service) Registry Number for simplified information retrieval.

ETIC is available as a subfile on TOXLINE (Toxicology Information Online) or provided by the National Institutes of Health's National Library of Medicine (NLM) through a nationwide NLM network of centers at more than 900 universities, medical schools, hospitals, government agencies, and commercial organizations.

Information from the ETIC file is also available from the Environmental Teratology Information Center, National Institute of Environmental Health Sciences, P. O. Box 12233, Research Triangle Park, North Carolina 27709. Commercial Phone Number (919) 541-3214, FTS Phone Number 629-3214.

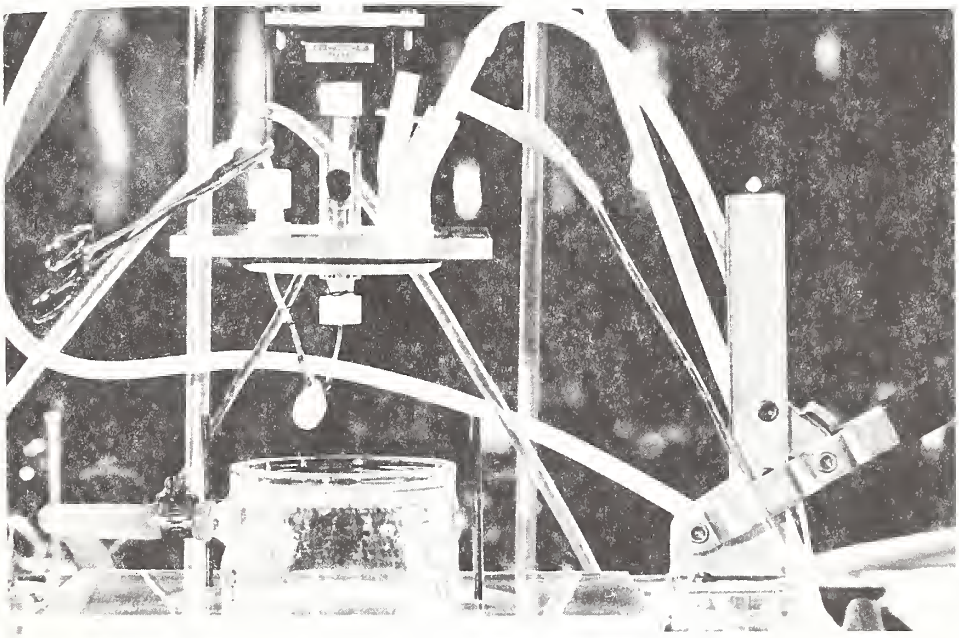
Risk Assessment

The risk assessment program at NIEHS is concerned with environmental agents as threats to man's health. Scientists involved with this program are currently extrapolating animal dose-response results to man. Realistic extrapolation of animal data is very necessary if results of animal studies are to be interpreted effectively in relation to human response.

Pharmacokinetics

The program focuses on finding better ways to study the rates and mechanisms of uptake, storage, persistence, metabolism, and excretion of environmental agents. Results from one animal species study can be extrapolated to other species, man, and specific organs, and can be used to predict and better understand the mechanisms of toxicity.

Because the liver and lungs are important sites of chemical entry and metabolism, NIEHS scientists are interested in isolating these organ systems to better understand the body mechanisms which handle environmental agents. The perfused organ technique allows scientists to study intact animal lungs and livers outside the body. In this way, the researchers are better able to ascertain the measured effects as specific to the organ. The investigators can then quantify and understand factors involved in the handling and degradation of toxic agents by these complex body organs.



A perfused animal heart is sustained by nutrients in the Inhalation Toxicology Section of the NIEHS. By isolating the organ from the whole animal, scientists can better investigate the organ-specific activity of particular environmental agents. The same procedure is used for the lung. (NIH Photo #NP-5)

THE SECOND NIEHS BIENNIAL SCIENCE SEMINAR

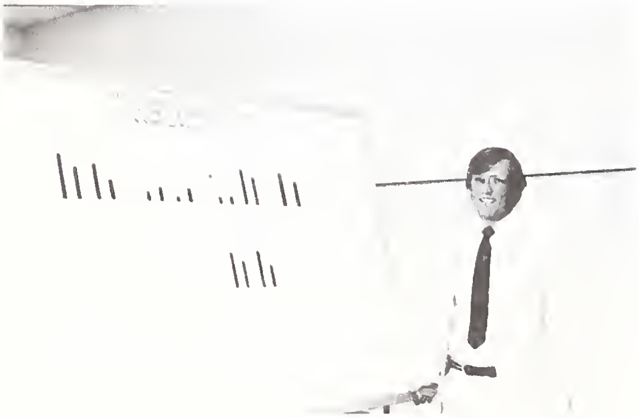
The 2nd Biennial Science Seminar of the National Institute of Environmental Health Sciences (NIEHS) was held at the North Carolina State University Jane S. McKimmon Center for Extension & Continuing Education, Raleigh, N.C.

The purpose of these seminars is two-fold: first, to bring scientists and research administrators from other Federal agencies, universities and industry together with the scientific and lay press. In this way, the researchers, press, and general public are provided with an in-depth view of the NIEHS research program. And second, the seminar provides an opportunity for the Institute scientific staff to interact and become more familiar with research programs being conducted in other laboratories.

D-18 THE CLARA CELL: INTERSPECIES VARIATION IN CELLULAR
DISTRIBUTION AND MORPHOLOGY
C G PLOPPER

(NIH Photo #NP-6)

(NIH Photo #NP-7)



(NIH Photo #NP-8)

INHALED CHRYSOTILE ASBESTOS IN THE LUNGS OF RATS
ANATOMIC LOCALIZATION AND ELEMENTAL CONTENT

(NIH Photo #NP-9)

TERATOGENICITY OF SELECTED ANTICONVULSANTS
J. Kao, E. Goulding, N. Brown, G. Shull, and S. Fabro
L.E.T

(NIH Photo #NP-10)

These photos from the science seminar show research conducted on:

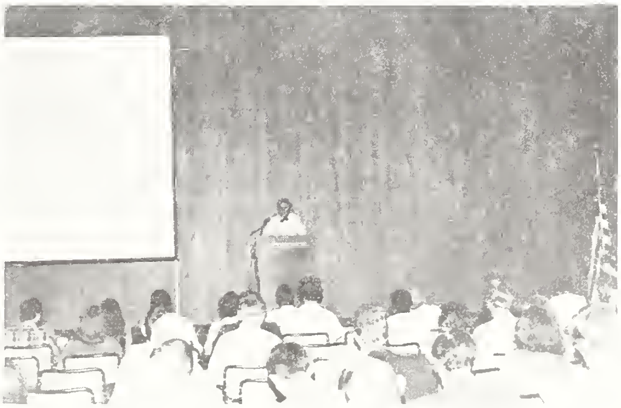
(#NP-6) a comparative study of the cellular characteristics of the Clara cell, a type of lung cell. Research emphasis is on its role in detoxification and carcinogen metabolism, and the interrelationship between these various functions:

(#NP-7) the effects of diethylstilbestrol (DES) on mammalian ovarian tissue, suggested to be an important fetal target tissue of the drug;

(#NP-8) male and female rats exposed to Kepone through the diet and tested for neurobehavioral dysfunction;

(#NP-9) the interaction of inhaled particles within the structures of the lungs and how they are distributed and exert their toxic influences;

(#NP-10) antiseizure agents which have been strongly implicated through clinical observations as human teratogens.

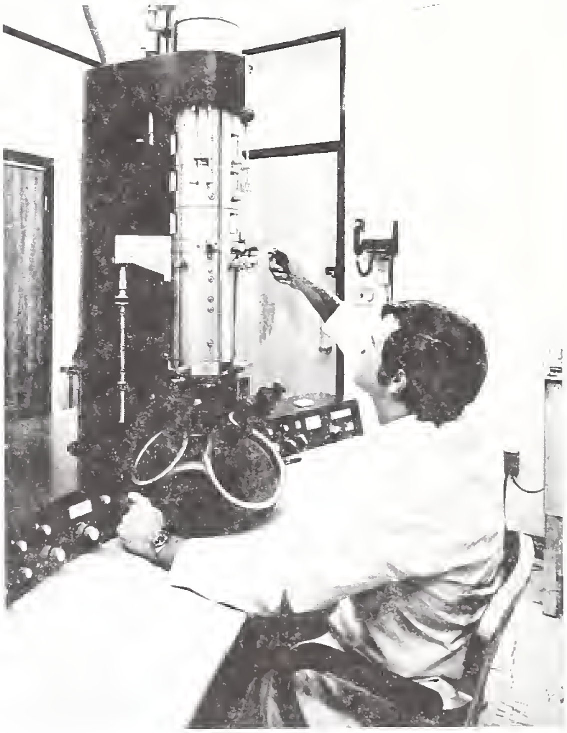


(NIH Photo #NP-11)

Chronic Organ Toxicity

The chronic organ toxicity program studies the identification of early biochemical or physiological changes in organ function caused by prolonged exposure to potentially toxic environmental agents. Some of the current ongoing programs are: transplacental effects of toxic agents in the development of specific organ functions; the possible role of trace metals, vinyl monomers, dioxins, and various components derived from energy-related technologies in the development of chronic organ disease.

The above is an electron micrograph of a rat kidney proximal tubule cell injected with cadmium-metallothionein. The effect of the complex on the kidney cell is studied by the Laboratory of Organ Function & Toxicology. (NIH Photo #NP-12)

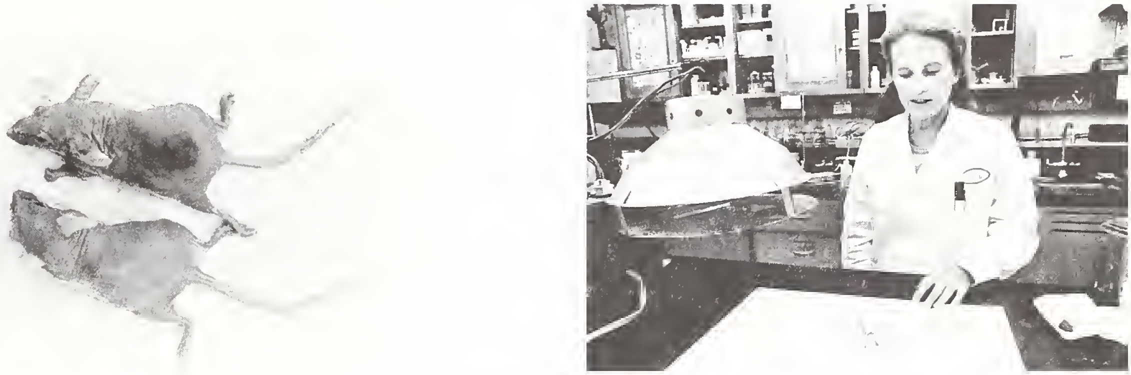


Dr. Bruce Fowler from the Laboratory of Organ Function & Toxicology is shown using the electron microscope to assess the morphological effects of cadmium-metallothionein on kidney proximal tubules. (NIH Photo #NP-13)

Behavioral Toxicology

Because behavioral changes can occur before significant body changes are observed, they can serve as advance warnings of toxicity. This program focuses on behavioral changes as indicators of environmental insults. For instance, some of the most significant adverse reactions to toxic agents are found affecting the brain's higher functions, as seen by the effect of carbon monoxide or heavy metals on the central nervous system.

The program seeks to determine whether the environmental contaminant primarily affects the human organism through ingestion, inhalation, or dermal contact. Physical agents such as noise, light, and non-ionizing radiation, are also being studied. New model systems, instruments, and techniques are, therefore, being developed to determine the behavioral and neurotoxic effects from exposure to these agents.



Hairless mice are studied by Laboratory of Pharmacology scientists to assess exposure effects from ultraviolet light on skin enzymes. Pictured with the mice is Roberta J. Pohl from the Laboratory of Pharmacology. (NIH Photo #NP-14 and 15)

Environmental Chemistry Branch

The formation of chlorinated products from aqueous organics during water treatment processes has recently been recognized as a major source of such chemicals in municipal water supplies. Naturally occuring materials like humic acid generally account for approximately 80 percent of the organic carbon dissolved in municipal drinking water supplies. These humics have been found to give low molecular weight chlorination products under typical water treatment plant conditions. Thus, a knowledge of humic acids' structure is fundamental to the understanding of halocarbon production in water supplies.

Humic acid is a complex organic molecule which must be degraded before mass spectrometric techniques can be applied. This project reports observations resulting from the application of gas chromatography/mass spectrometry (GC/MS) using electron impact (EI) or isobutane positive ion chemical ionization and mass-analyzed ion kinetic energy (MIKE) spectrometry using collision-induced dissociations (CID) of ions produced by butane positive chemical ionization (BPCI) and direct probe sample introduction.

Pulmonary Toxicology

Pulmonary toxicology is a relatively new NIEHS program concerning the prevention of environmentally-caused respiratory diseases. Research emphasis is placed on studying the mechanisms of pulmonary biology and pathology in appropriate experimental models.

Marine and Freshwater Biomedicine

Because marine and freshwater species are frequently susceptible to pollutants, the Institute's program studies the accumulation of pollutants in aquatic species serving as human food sources. Possible factors which affect that accumulation are also being investigated. One program goal is the study of aquatic species as early warning systems or sources of pollution dangerous to human health.

Within NIH and DHEW, NIEHS has established Marine and Freshwater Biomedical Centers. The centers integrate, coordinate, and foster interaction and cooperation among established interdisciplinary investigators conducting research clearly related to environmental health. This cooperation enables the Institute to build upon existing expertise and resources. The potential for accomplishments is thereby increased through this approach as opposed to support of individual projects.

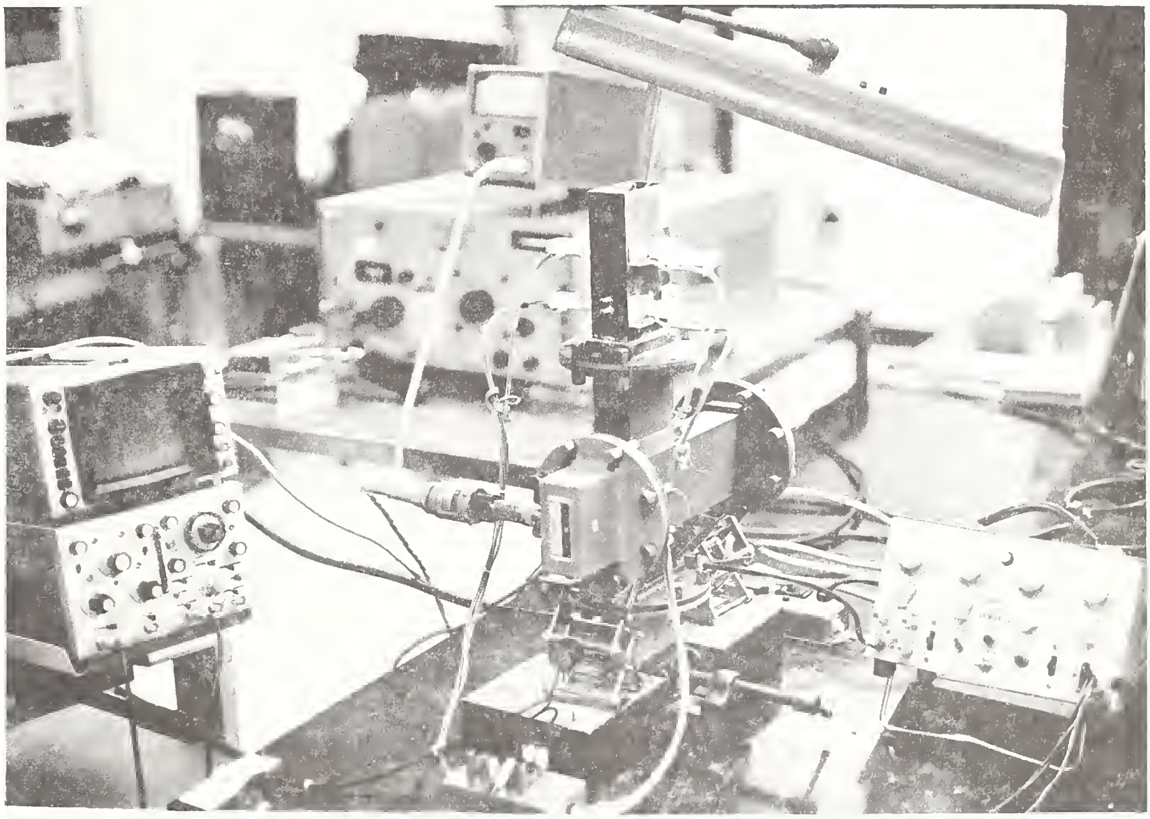
Epidemiology

The Epidemiology program studies disease patterns in the population. Some of the project areas include population and animal monitoring, statistical epidemiology, and the integration of these studies into the Institute's intramural biological research programs. For instance, statistical epidemiologists are concerned with the distribution of health indices over time and space, and their association with patterns of environmental exposures.

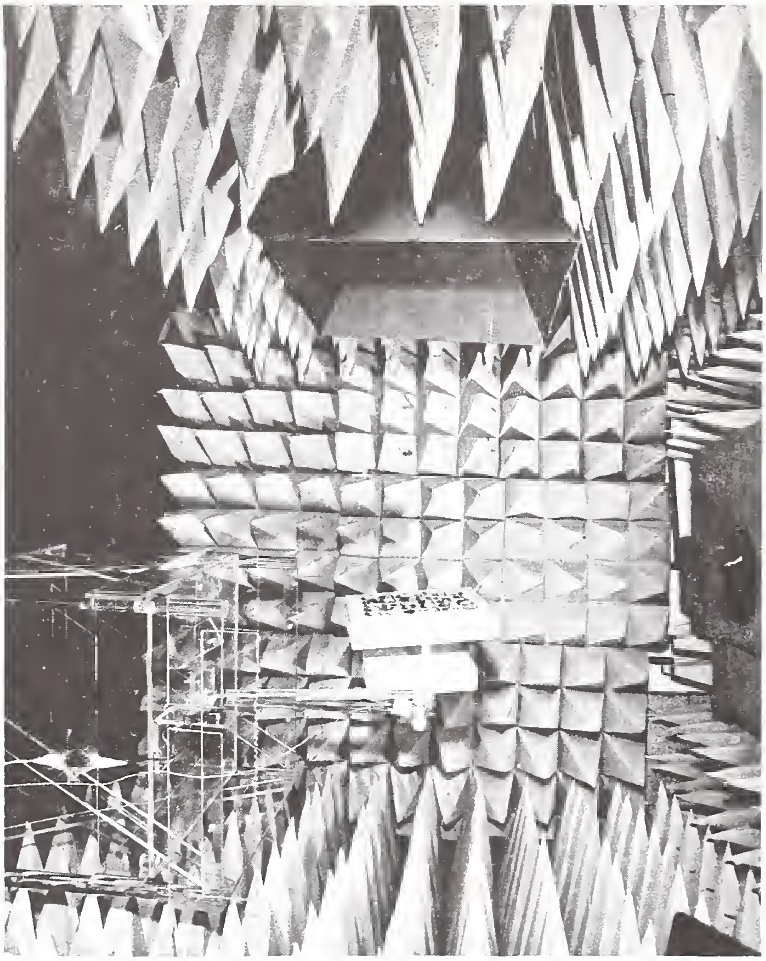
Laboratory of Environmental Biophysics

This area is primarily concerned with the biological effects of physical factors present in our environment. Presently, the Laboratory is focusing research on the two areas of non-ionizing radiation (microwaves) and noise (both auditory and nonauditory effects).

One of the special concerns of non-ionizing radiation research is the effect f prolonged low level exposure to microwaves. Researchers are studying the ffect of long-term exposure of experimental animals to 915 MHz and 2450 MHz icrowave radiation on their central nervous systems (CNS) and behavior, and earning the effect of 60 Hz (cycle) fields from high voltage transmission lines on the CNS of mammals. The 2450 and 915 MHz microwave radiation is of concern because it is at these frequencies that microwave ovens operate.



A waveguide exposure system is used in the Laboratory of Environmental Biophysics to determine the effects of microwaves on isolated nerve preparations. (NIH Photo #NP-16)

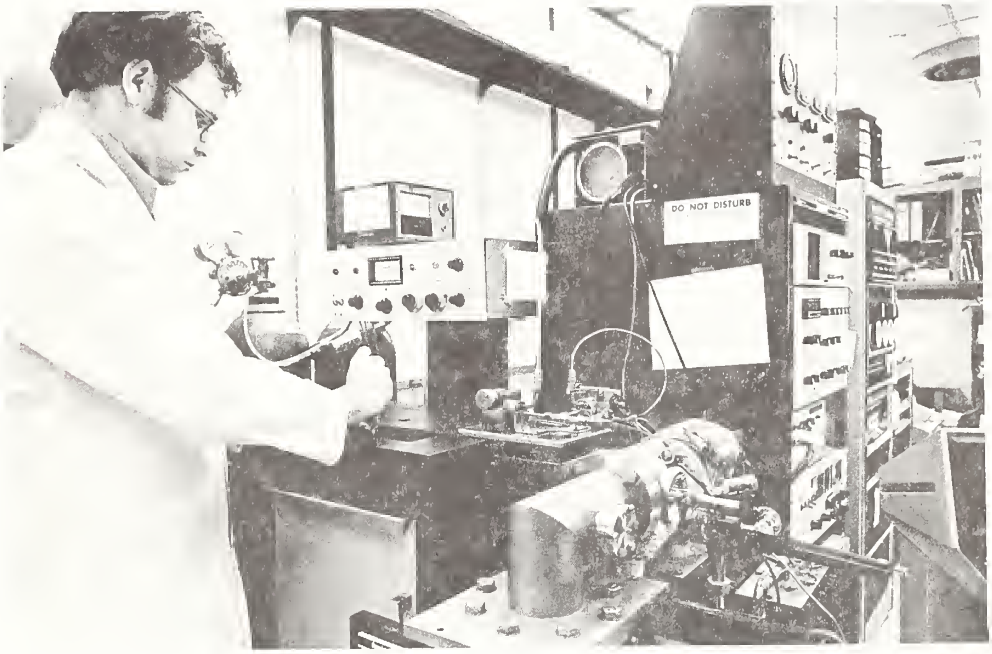


Microwave exposure of Japanese quail embryos is studied to determine developmental and behavioral effects in the Laboratory of Environmental Biophysics.(NIH Photo #NP-17)

The non-ionizing radiation program also deals with the development of microwave exposure systems for bioeffects research, development and testing techniques for measuring microwave energy absorption, determination of the effects of microwaves on isolated nerve preparations, and investigation of how 2450 MHz radiation interacts with biological systems at all levels. In studies on Japanese quail, a small decrease in fertility was observed when males exposed *in ovo* to microwaves were mated with either control or exposed females. Also, preliminary results suggest that exposure of pregnant rats to 915 MHz radiation does not alter the relative numbers of viable offspring and stillborns.

The noise research program is directed toward a better understanding of the physiological workings of the inner ear and the basic transduction mechanism whereby sound is converted into electrical nervous impulses.

Some of the areas currently being investigated are: the effects of noise and ototoxic agents on the electrolyte concentration of cochlear fluids and ionic fluxes across the cochlear partition; the development of an optic fiber motion detector for auditory system measurements; development of electrophysiological techniques to recover speech from the cochleas of live, anesthetized guinea pigs; the effect of ototoxic insult on the coding of complex signals in the auditory system; and, the development of an impact noise generator for hearing loss studies.



Dr. J. Ronald Haas, Environmental Chemistry Branch, NIEHS, prepares to operate the negative ion chemical ionization spectrometer, the first such equipment to be used in environmental health science research.(NIH Photo #NP-18)

Synergism

Research in synergism seeks to improve detection of environmental contaminant interaction and their hazards, and further, to predict the extent and nature of their combined effect on human health. Many real hazards can occur through interaction of environmental agents and metabolic processes within the body. Such interactions may result in enhanced toxicities or in quantitatively different kinds of toxicity.

Conclusion

Environmental health research asks a myriad of diverse and complicated questions. Using knowledge gained through research and risk benefit analysis, a balance between public health benefits and true societal need must be sought. Only through basic research can knowledge be gained to identify toxic agents and to determine how they exert their harmful effects. NIEHS scientists are dedicated to producing this information.

###

Editors of publications may request a glossy print of the photographs that appear in this Portfolio.

Ms. Maureen Napper
National Institutes of Health
Building 31, Room 2B-10
Bethesda, Maryland 20205

Dear Ms. Napper:

Please send me one glossy print of the photograph from the list below:

CP ______

NP #1 ______
NP #2 ______
NP #3 ______
NP #4 ______
NP #5 ______
NP #6 ______
NP #7 ______
NP #8 ______
NP #9 ______

NP #10 ______
NP #11 ______
NP #12 ______
NP #13 ______
NP #14 ______
NP #15 ______
NP #16 ______
NP #17 ______
NP #18 ______

Name: ______________________
Title: ______________________
Publication: ______________________
Address: ______________________
City, State, Zip: ______________________
Telephone: ______________________

NIH LIBRARY
Amazing Research.
Amazing Help.

http://nihlibrary.nih.gov

10 Center Drive
Bethesda, MD 20892-1150
301-496-1080

WERT
BOOKBINDING
Grantville, Pa.
Nov—Dec 1985
We're Quality Bound

NIH LIBRARY
3 1496 00276 8581